MEDICINE

CVS / RS / RENAL

VOL- 1

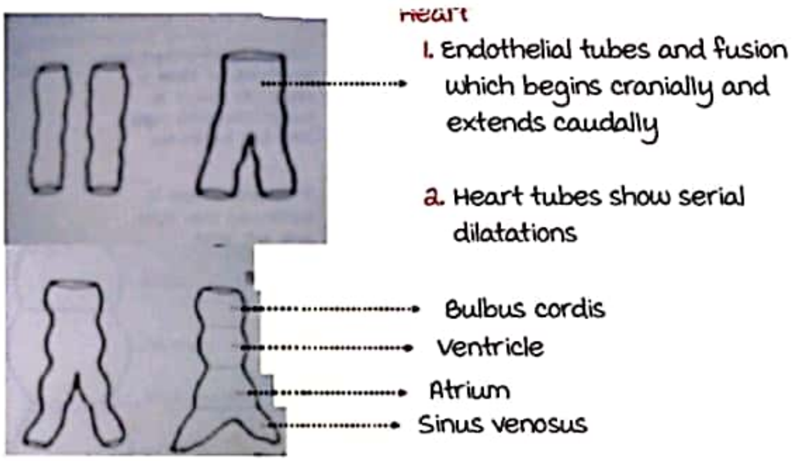
CARDIOLOGY BASICS: ANATOMY

1

Development of the heart

00:01:28

- Angiogenic clusters in splanchnic mesoderm → 2 endothelial / cardiac tubes


Heart

1. Endothelial tubes and fusion which begins cranially and extends caudally

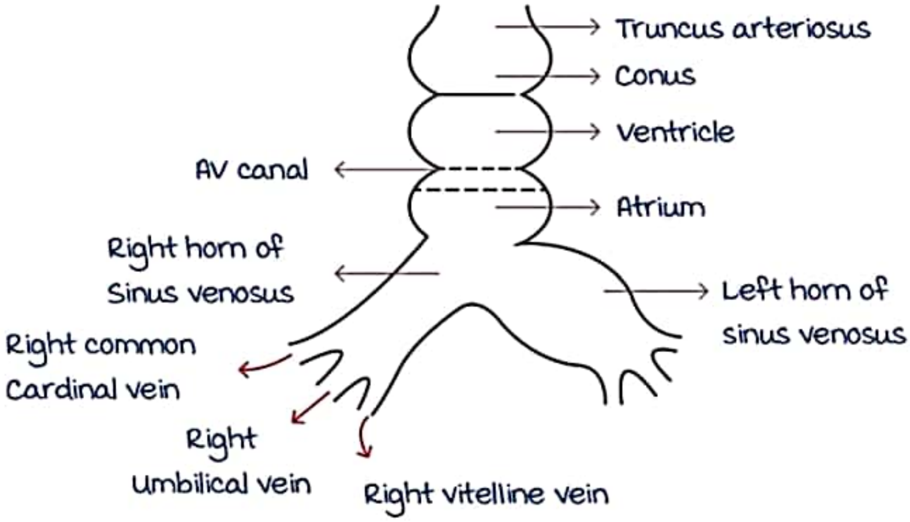
2. Heart tubes show serial dilatations

Bulbus cordis
Ventricle
Atrium
Sinus venosus

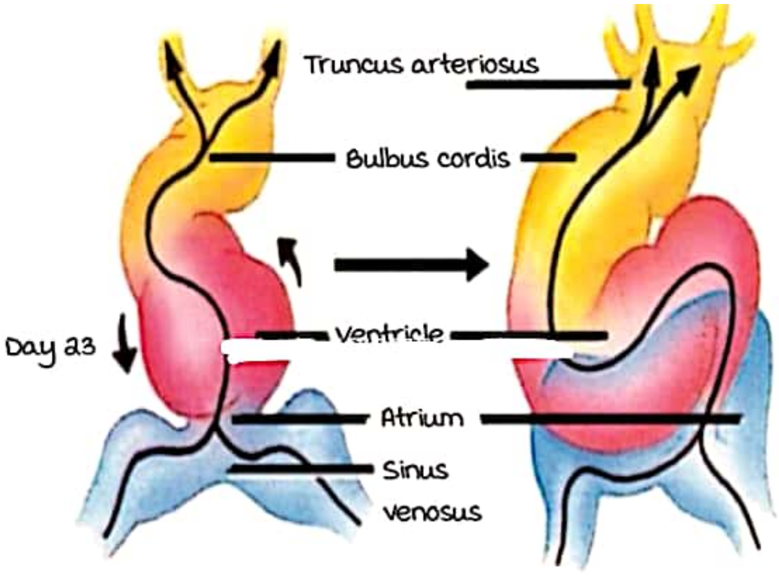
- Fusion to form single cardiac tube: Day 19

- Series of dilatations occur:
  - → Truncus arteriosus
  - → Bulbus / conus cordis
  - → Primitive ventricle
  - → Primitive atria
  - → Sinus venosus
    - → Left horn
    - → Right horn

Cranial ↓ Caudal


Truncus arteriosus
Conus
Ventricle
AV canal
Atrium
Right horn of Sinus venosus
Left horn of sinus venosus
Right common Cardinal vein
Right Umbilical vein
Right vitelline vein

Active space



- Heart begins to contract : Day 22
- Looping: Day 23

Fate of dilatations

00:07:34

- Left horn of sinus venosus : Coronary sinus
- Body of sinus venosus
  Right horn of sinus venosus } smooth part of right atrium → Sinus venarum
- Primitive atria : Rough part of atria
- Primitive ventricle : Rough part of ventricles
- Bulbus cordis: Smooth part of ventricles
- Fusion of endocardial cushion separates
  - → Atria
  - → Ventricles
- Truncus arteriosus
  - → Aorta
  - → Pulmonary trunk

  } Formed by Spiral septum / Conotruncal septum ↓ (a neural tube derivative)

Active space

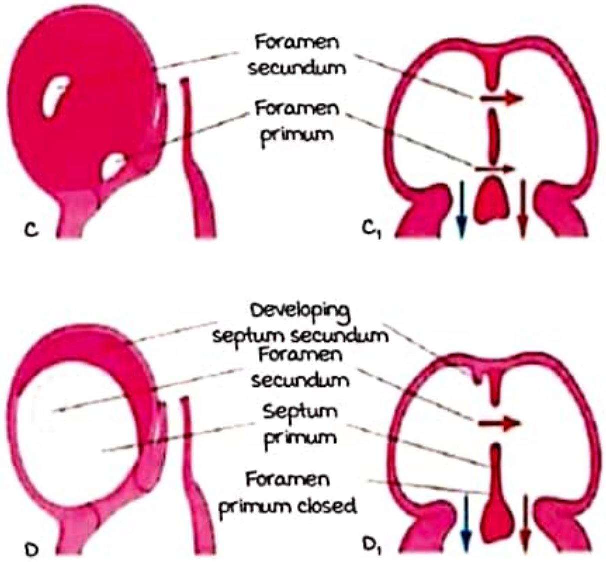
- Spiral septum
  - → Anteriorly displaced → Tetralogy of Fallot (TOF)
  - → Absent → Persistent truncus arteriosus
  - → Failure of fusion of spiral septum → Transposition of Great Arteries (TGA)

Development of inter-atrial septum

00:13:34

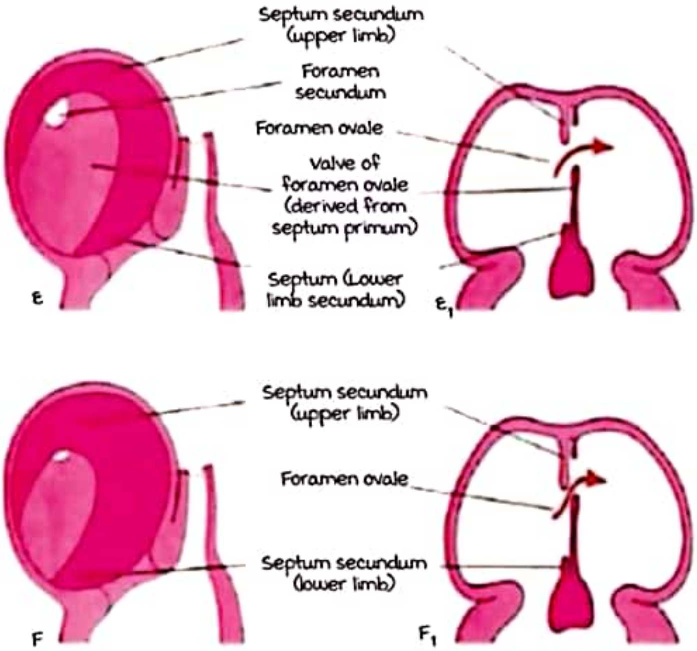
Atrial partitioning I

Red arrows-Well oxygenated blood   Blue arrows-Poorly oxygenated blood


Foramen secundum
Foramen primum
C
C₁
Developing septum secundum
Foramen secundum
Septum primum
Foramen primum closed
D
D₁

- Foramen secundum: Perforates septum primum, allowing shunt
- Septum secundum grows down, overlapping foramen secundum

Atrial partitioning II


Septum secundum (upper limb)
Foramen secundum
Foramen ovale
Valve of foramen ovale (derived from septum primum)
Septum (Lower limb secundum)
E
E₁
Septum secundum (upper limb)
Foramen ovale
Septum secundum (lower limb)
F
F₁

- Septum secundum grows down, overlapping foramen secundum
- Foramen ovale: Between septum primum & septum secundum

- After birth : Septum primum → Fossa ovalis
  Septum secondum → Limbus fossa ovalis

Vascular development

00:18:05

I) Arteries

- Dorsal aorta connected to aortic sac by 6 arch arteries
- 1st arch artery → Maxillary artery
- 2nd arch artery → Stapedial artery
- 5th arch artery → Regresses
- Left Horn of aortic sac
- Left 4th arch artery
- Left Dorsal aorta

} Aortic arch

- Right 4th arch artery
- Right Dorsal aorta
- Right 7th cervical intersegmental artery

} subclavian artery

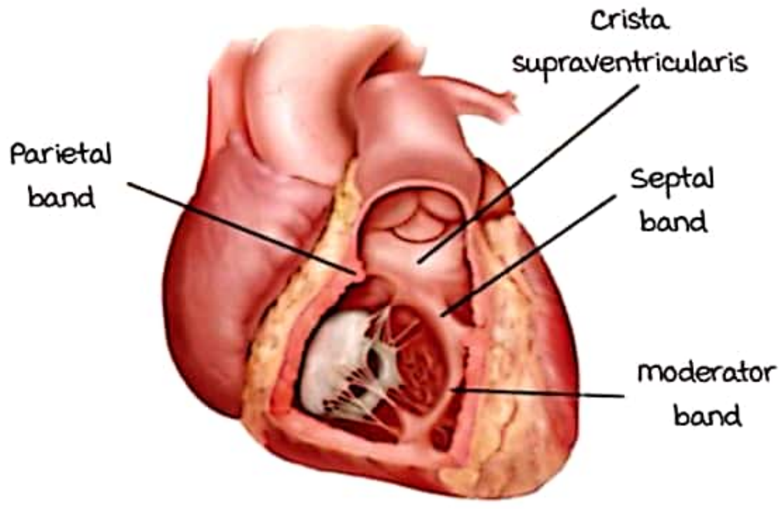
- Right horn of aortic sac → Brachiocephalic trunk
- Left 7th cervical intersegmental artery → Left subclavian artery
- Proximal part of 3rd arch → Common carotid artery
- Distal part of 3rd arch artery + cranial part of dorsal aorta → Internal carotid artery
- Left 6th arch artery
  - → Proximal → Pulmonary artery
  - → Distal → Ductus arteriosus

Right 6th arch artery → Right pulmonary artery

II) Veins:
- Right common cardinal vein: Part of SVC
- Right umbilical vein: Regresses
- Right vitelline vein: Part of IVC

Valves and chambers of heart

00:32:09

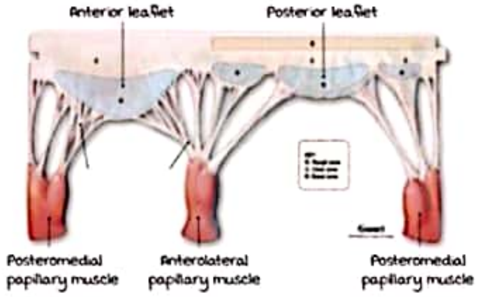


- Crista supraventricularis separates tricuspid valve (TV) and pulmonary valve (PV)
- Lambl's excrescences → Aortic valve (AV)
- Right atrium
  - → Smooth part → Sinus venarum
  - → Rough part → musculi pectinati
  - } Separated by: Crista terminalis
- False tendons → In LV
- Coarsely trabeculated apical zone → In RV
- Tricuspid valve: 5 parts
  - → Annulus
  - → Leaflets / Cusps : 3
  - → Commissures
  - → Chordae tendineae
  - → Papillary muscles

  Valve with triangular orifice and numerous septal attachments

- Mitral valve:
  - same 5 parts as TV; Leaflets / Cusps: 2
  - Anterior leaflet → Large, in fibrous continuity with aortic valve
  - Posterior leaflet → Small, prone for dilatation and prolapse
- Posteromedial papillary muscle has only one blood supply → RCA

  ∴ RCA occlusion → Causes acute MR due to papillary muscle rupture


Anterior leaflet
Posterior leaflet
Posteromedial papillary muscle
Anterolateral papillary muscle
Posteromedial papillary muscle

- Annulus:
  - Fibrous ring, works as sphincter
  - Ensures complete closure of leaflet during systole
  - Promotes valve competence
  - Annular dilatation causes MR / TR

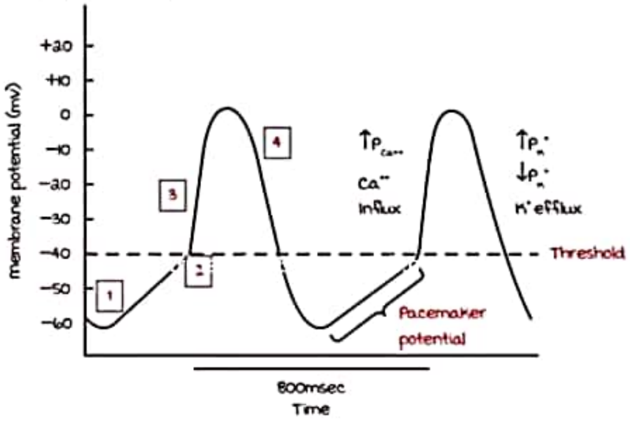
Terms used 00:01:21

- Chronotropy: Heart rate (SAN)
- Inotropy: myocardial contractility (Ventricular action potential)
- Dromotropy: Cardiac conduction velocity
- Bathmotropy: Cardiac excitability
- Lusitropy: Cardiac relaxation

Sinoatrial node (SAN) action potential 00:02:52

- Pacemaker:
  - Responsible for automaticity (ability to generate impulse even in the absence of an external stimulus)
  - Potential generated is pacemaker potential
  - In SAN : Slope of pacemaker potential is maximum
    Able to generate impulses at highest rate = 100/ min
    (Parasympathetic mediated decrease in pacemaker potential i.e; Resting vagal tone is responsible for HR to be 72/min instead)
  - Also, in AVN, His – Purkinje system, atrial cells near ostium of Coronary sinus
- SAN action potential: A/K/A pacemaker potential / pre-potential/ restless membrane potential/ Spontaneous diastolic depolarisation/ Slow-response action potential

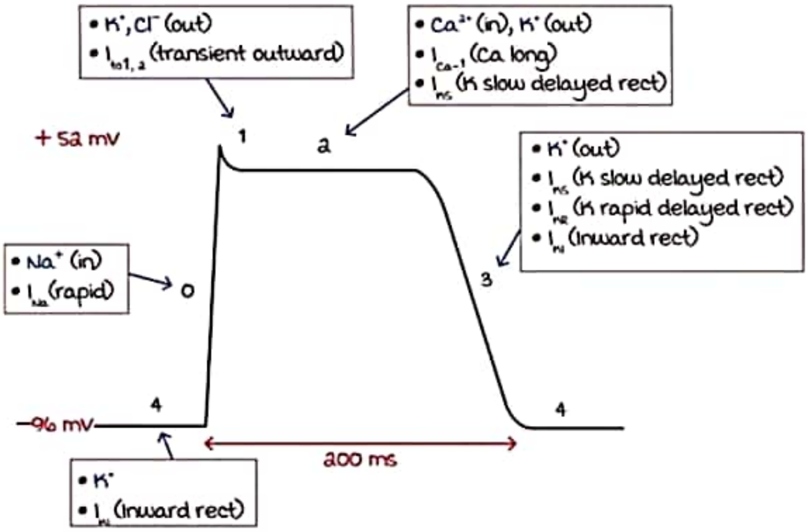
1. 'Funny' sodium channels (I_f channels) are open ($\uparrow P_{Na^+}$); and closing K^+ channels.
2. Transient Ca^{2+} (T-type) channels open, pushing the membrane potential to threshold.
3. Long-lasting Ca^{2+} (L-type) channels open, giving rise to the action potential.
4. Opening of K^+ channels, ($\uparrow P_{K^+}$), and closing of Ca^{2+} (L-type) channels, hyperpolarising the cell



- Determined by:
  - Funny current (Na^+ channels)
  - Transient 'T- type' Ca^{2+} channels
  - Transient out flow K^+ channels (closing)/ inward rectifying K^+ channels (opening)
- most important :
  - Inward rectifying K^+ channels > Transient outflow K+ Channels > Funny current (Na^+ channels) > Transient T-type Ca 2+ channels
- Slope of pacemaker potential: - mostly affected by ANS
  - → Sympathetic system → ↑Slope, shift to left, ↑HR
  - → Parasympathetic system → ↓Slope, shift to right, ↓HR
- Depolarization: - By, slow inward 'L- type' Ca^{2+} channels
- Repolarisation: - By, delayed rectifier K^+ channels
- Funny current:
  - mostly Na^+ channels
  - HCN channels (Hyperpolarization activated cyclic nucleotide channels)
  - Also seen in, rods, cones, olfactory epithelium
  - Ivabradine
    - → Blocks funny current
    - → HR without affecting BP
    - → S/E:- Visual disturbances

Ventricular action potential

00:19:59


• K^+, Cl^- (out)
• $I_{to1,2}$ (transient outward)
• Ca^{2+} (in), K^+ (out)
• I_{Ca-L} (Ca long)
• I_{Ks} (K slow delayed rect)
+ 52 mV
1
2
• K^+ (out)
• I_{Ks} (K slow delayed rect)
• I_{Kr} (K rapid delayed rect)
• I_{K1} (Inward rect)
• Na^+ (in)
• I_{Na} (rapid)
0
3
4
−96 mV
4
200 ms
• K^+
• I_{K1} (Inward rect)

- Phase 0 → Depolarisation; Phase I → Early repolarisation; Phase 2 → Plateau Phase; Phase 3 → Late repolarisation; Phase 4 → RMP (Na^+-K^+ ATPase)

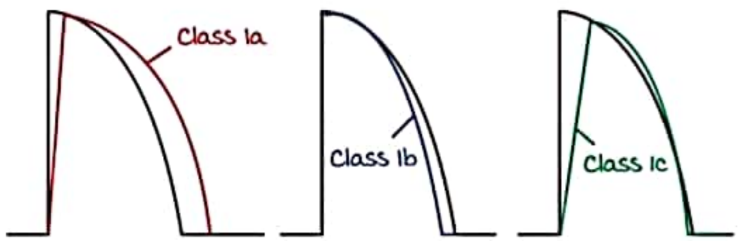
Vaughan williams classification of anti – arrhythmic agents

00:25:36

- Based on predominant action:
- Class I : – Acts on phase 0 of ventricular AP (Na^+ channel blockers)
  - → I_a:– moderate ↓ in $\frac{dv}{dt}$ of phase 0, ↑ QRS & QT
    - Eg:– Quinidine, Procainamide
  - → I_b:– mild ↓, ↓ QT ; Eg:– Lignocaine
  - → I_c:– marked ↓, ↑↑ QRS
    - Eg:– Propafenone; Flecainide

Class I Antiarrhythmic drug effects

On the ventricular action potential:



- Class II : – On Phase 4 (β blockers)
- Class III : – On Phase 3 (K^+ channel blockers)
  - maximally prolong QT
  - B : Bretylium
  - I : Ibutilide
  - D : Dofetilide
  - A : Amiodarone
  - S : Sotalol (K+ channel blocker → is predominant anti – arrhythmic action)
- Class IV : – On Phase 2 (CCBs)

→ myocardial O_2 consumption is 8 ml/ 100g/ min

→ (O_2 consumption ∝ EDV) ⇒ In angina ; Nitrates ↓ EDV,

→ 70/30: Fatty acid /carbohydrate → Fuel for cardiac myocytes ⇒ pFox ⊖ (Ranolazine; Trimetazidine)used in angina

→ Resting coronary flow = 60 – 90 ml/100g/min or 225 ml/min

→ Frank – Starling law: – Force of contraction is proportional to initial length of muscle fibre

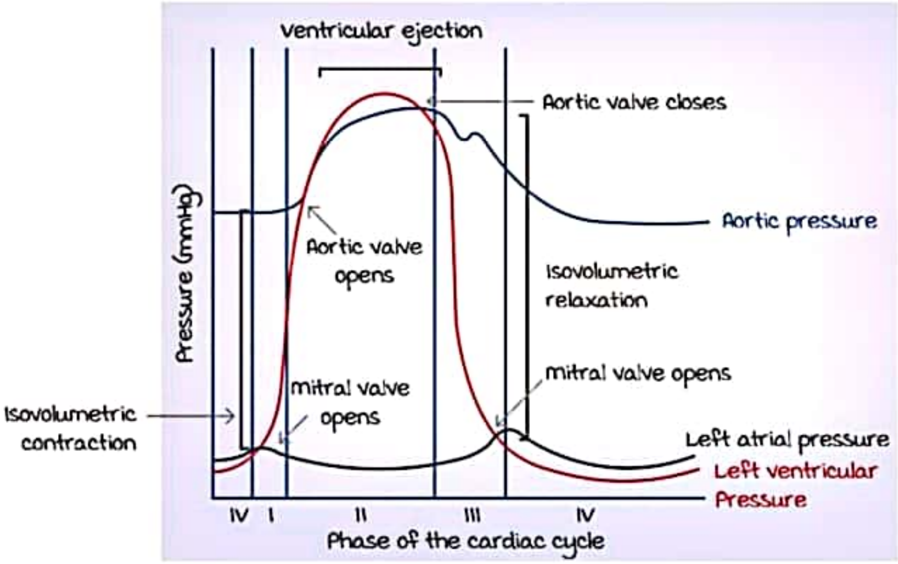
→ $EF = \frac{EDV - ESV}{EDV} \times 100 = \frac{SV}{EDV} \times 100 \approxeq 65\text{-}70\%$

Cardiac cycle

00:42:45

	Systole	Diastole	
Atria	0.1	0.7	0.8 s
Ventricle	0.3	0.5	0.8 s

cardiac cycle



- Atrial systole:
  - 70% ventricle filled with blood beforehand (∴ AV valves open)
  - For additional 30% → atrium contracts → a wave in JVP → S_1 Soon after atrial systole due to closure of AV valves

- Isovolumetric contraction: – At the end ; Pulmonary and aortic valves open
- Rapid ejection and reduced ejection follow.
- Following which aortic and pulmonary valves close (S_2)in Protodiastole
- Isovolumetric relaxation: – At the end; AV valves open
- Rapid filling and reduced filling follow.

→ maximum pressures that can be achieved;
RA = 3-5mm Hg; LA = 8 mmHg
RV = 25 mmHg; LV = 80 mmHg

PULSE

Pulse : definition 00:02:08

- Arterial pulse wave :
  - Pressure wave, due to ejection of blood during LV systole; Originates in aorta
  - Travels at 5 m/s (Column of blood at 40-50 cm/s) faster → than column of blood, so transmitted to peripheral vessels
- Character and contour of pulse → Best appreciated in carotid artery > brachial artery

Waveform 00:04:41

- Systolic part : 2 systolic waves.
- Percussion wave (P)
  - Due to pressure generated within LV during contraction → Transmitted to aorta (aortic compliance dependent)

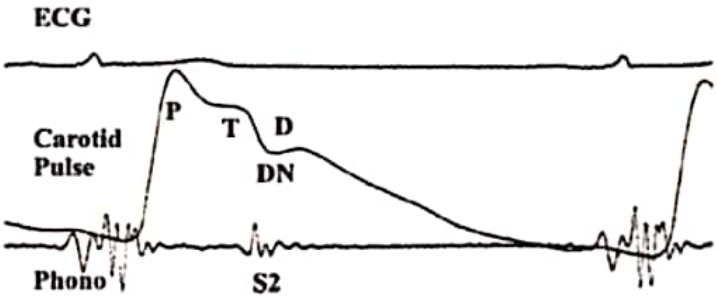


Fig. 1. simultaneous recordings of ECG, carotid pulse tracing, and phonocardiogram. The carotid pulse shows the percussion wave (P), the tidal wave (T), and the dicrotic wave (D), which follows the dicrotic notch (DN)

- Anacrotic notch:
- Tidal wave(T):
  - Due to cardiac output (CO) i.e volume → Also dependent on arterial stiffness

→ Both P and T occur after S_1 and before S_2

- Dicrotic notch (DN) / Incisura
  - Corresponds to S_2

- Diastolic part:
  - Dicrotic wave: Reflected wave from periphery → Due to Peripheral Vascular Resistance (PVR)

→ Changes seen as pulse transmits peripherally:
- Upstroke becomes steeper, Anacrotic notch becomes less apparent, Incisura replaced by a smooth dicrotic notch

Brachiofemoral delay

00:14:16

- Normal delay for pulse wave transmission :
  - Carotid : 30 milli sec
  - Brachial : 45 milli sec
  - Radial : 80 milli sec
  - Femoral : 75 milli sec
- Important for diagnosing coarctation of aorta (COA)

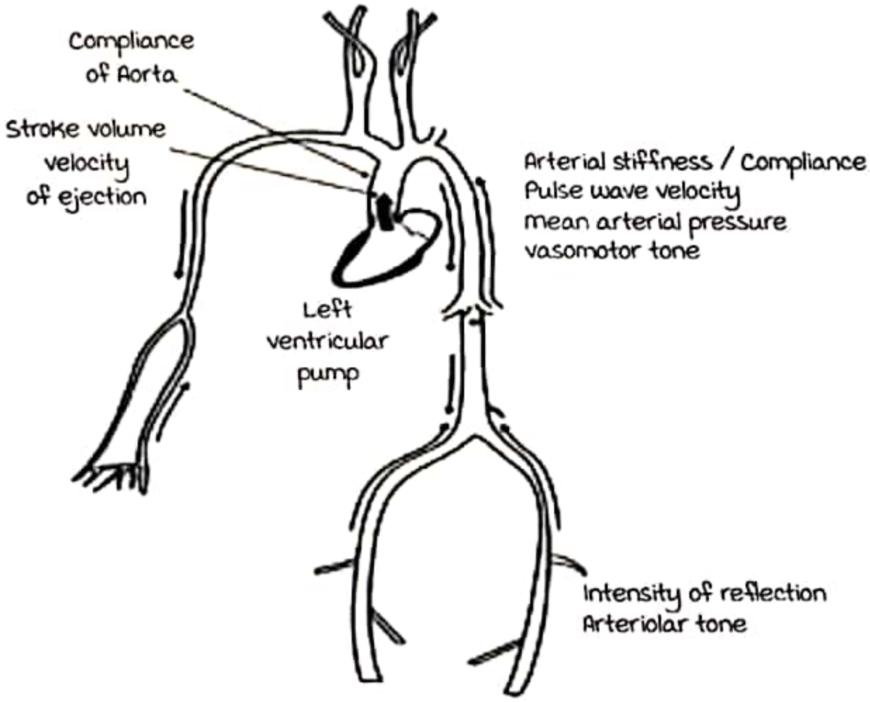
Pulse wave velocity

00:14:59

- Ejection velocity
  - → Pressure = $\frac{dp}{dt}$
  - → Volume

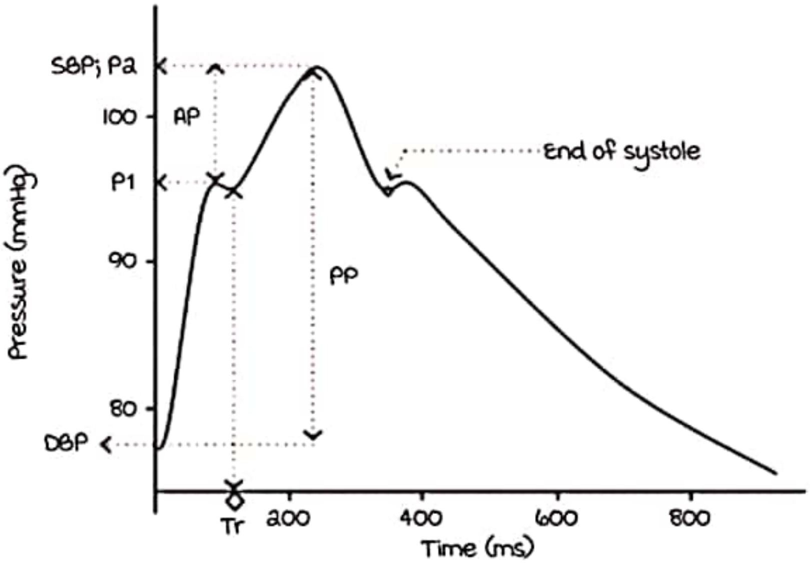
  } Compliant aorta

- Reflection → Dicrotic wave (due to arteriolar tone / PVR predominantly)


Compliance of Aorta
Stroke volume
velocity of ejection
Arterial stiffness / Compliance
Pulse wave velocity
mean arterial pressure
vasomotor tone
Left ventricular pump
Intensity of reflection
Arteriolar tone

- Pulse wave velocity:
  - Dependent on mean Arterial Pressure (MAP) or arterial stiffness

⇒ Elderly patient with stiff vessels / Patient with systemic HTN
→ ↑ Pulse wave velocity



- Stiff arteries → ↑ Pulse wave velocity → Reflected wave arrives earlier (i.e; in systole) → Augments central systolic pressure → Late systolic peak (Tidal wave) ⇒ Amplitude of tidal wave > percussion wave

- Elderly ↑
  - → ↑SBP
  - → ↓DBP
  - → Wide Pulse Pressure

  } Compromised coronary perfusion

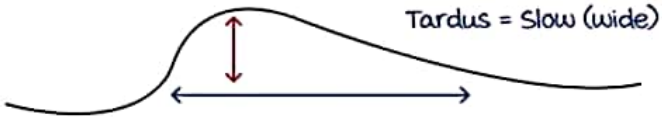
- Augmented pressure (AP):
  - → (T−P)
  - → Systolic pressure is towards higher side

Active space

Amplitude of pulse

- Rate, rhythm, volume → Appreciated well in radial artery
- Volume / Amplitude:
  - i) Hyperkinetic pulse: – High volume / High amplitude pulse
    - Causes: – Conditions with ↑ CO
      - → Anemia
      - → Pregnancy
      - → Beri beri
      - → Thyrotoxicosis
    - – ↓ PVR (Dicrotic wave becomes less prominent)
    - ↑ upstroke (predominantly tidal wave)
    - High amplitude pulse but ↓CO → Complete heart block (∴ ↓HR)
    - Associated with aortic run-off
      - → Eg:- AR, aorto – pulmonary window, PDA
      - → Called Water hammer pulse / Collapsing pulse / Corrigan's pulse / Watson's pulse / Dancing pulse (∵ Wide PP ⊕)
  - ii) Hypokinetic pulse: – Low volume / Low amplitude pulse
    - Causes: – ↓ CO, LVF
      - → Cardiogenic shock
      - → Hypovolemic shock
    - Upstroke may be high, but pulse amplitude may be Ⓝ/low
      - → HOCM [SAM → Systolic anterior motion of mitral valve leaflet]
      - → Severe MR
- Pulsus parvus et tardus / Anacrotic pulse :
  - Severe AS
  - AS
    - → Ejection velocity ↑ → ↓ lateral pressue → Slow rate of rise of pressure
    - → Volume in aorta less → Less upstroke

Pulsus parvus et tardus



Parvus = Weak (low peak)

Tardus = Slow (wide)

Rate of pulse

00:38:53

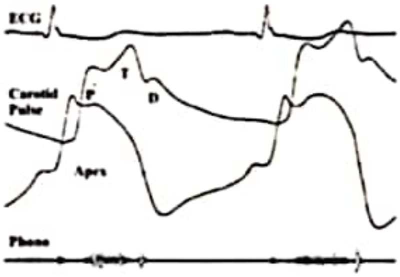
- Sinus tachycardia:
  - → High output states
  - → Hypovolemic shock / Cardiogenic shock
  - → myocarditis
  - → AWMI
- Faget sign:
  - 1°F ↑ in temperature ↑ PR by 10 bpm
  - If doesn't ↑ → relative bradycardia
  - Causes:
    - → Infectious : - Typhoid, legionellosis, Q fever, psittacosis,
      - Rarely : malaria, dengue
    - → Non-infectious: - Drugs: -β-blockers,
      CCB - Verapamil, Diltiazem
- Sinus bradycardia: - Hypothermia, myxedema, raised ICT (Cushing's reflex), RCA → IWMI, drugs → β blockers, CCBs, digoxin

Contour abnormalities in pulse

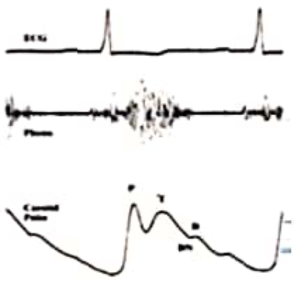
00:43:20

- Pulsus bisferiens:
  - 2 peaks in systole
  - In severe AR, AR+AS, HOCM.
  - Carotid is best (but bruit may be present) → ∴ radial artery is preferred
- AR:
  - High stroke volume → ↑pressure pulse wave → Large amplitude → Dip in pressue during systole [2 peaks in systole → Tidal wave higher amplitude]

Pulsus bisferiens in Severe AR with AS



- HOCM:
  - Hypercontractile ventricle
    - → Pumps blood in aorta → middle of systole: SAM ↓ Aortic pressure ↓
    - → Second peak:- In late systole
    - → T may not be > P



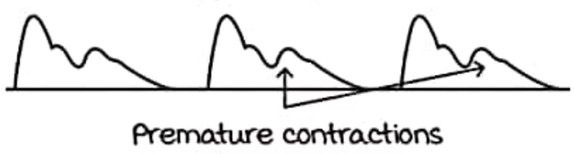
- Dicrotic pulse: 1 peak in systole, and in diastole → very prominent dicrotic wave (↑ PVR)
  Causes: - Conditions with ↓ CO, severe LVF; etc

Rhythm of pulse

00:51:23

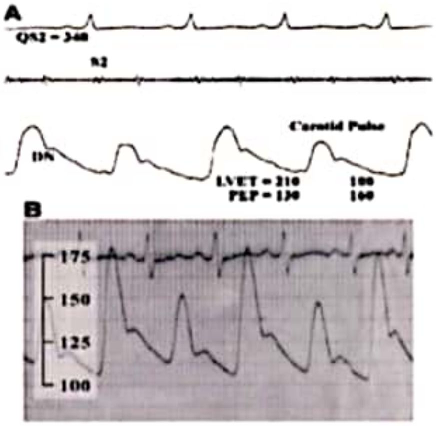
- Types:
  - Regular
  - Irregularly irregular: - variation cannot be predicted, Atrial fibrillation
  - Regularly irregular: Predictable variation
    In, Pulsus bigeminy (due to ventricular premature complex)
    - → Ⓝ beat alternating with premature contraction
    - → Stroke volume of premature beat is very low

Bigeminal pulse



- SV of the premature beat diminished, and pulse varies in amplitude accordingly
- May masquerade as pulsus alternans - but regularly irregular rhythm

- Pulsus alternans: – most specific and most characteristic finding of LVF
  - Alternating high and low amplitude pulse wave
    Always regular
  - Sphygmomanometer is used to detect
  - Extrasystole → Premature depolarization → release of more Ca^{2+} from sarcoplasmic reticulum even before Ca^{2+} released during previous beat could be taken back → Post premature beat



- Post extra systolic pulse:
  - Following ventricular premature complex → Longer compensatory pause → more diastolic filling → ↑End diastolic volume (EDV) → ↑Stroke volume → ↑pulse volume
  - In HOCM: Post extra systolic pulse volume doesn't ↑due to dynamic obstruction (SAM) → Brockenbrough sign

Warning: Not all points are covered in the notes, especially conceptual explanations. Please use the notes in conjunction with Marrow Edition 4 videos.

Pulsus paradoxus 01:02:38

- Normally, systolic BP ↓ by 10mm during inspiration.
  Exaggerated fall i.e; > 10mmHg : Pulsus paradoxus / Pulsus normalis aggregans

Warning : Not all points are covered in the notes, especially conceptual explanations. Please use the notes in conjunction with Marrow Edition 4 videos.

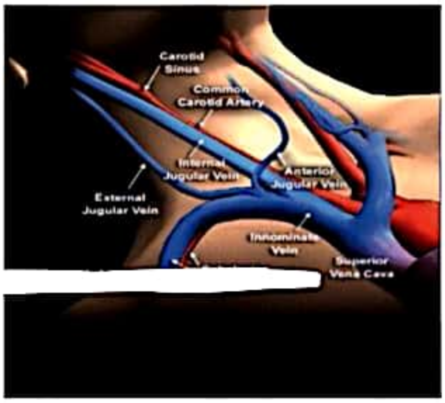
- → In cardiac tamponade:- Preferential filling of right-side during inspiration and left side during expiration (mostly septal filling)
  → blood in right ventricle pushes the septum towards left
  → Left ventricle CO low → Pulsus paradoxus
- → In constrictive pericarditis: - In 1/3rd of patients; pericardium thickened
- → COPD:- ↑blood pooling in pulmonary vasculature due to hyperinflated lung; ↓ venous return to Ⓛ side → ↓ CO
- → Pulmonary embolism:- Pulmonary intravascular volume expands
- → Venacaval obstruction by thrombi : - ↓right heart and pulmonary filling
  → ↓left heart filling
- → Obesity

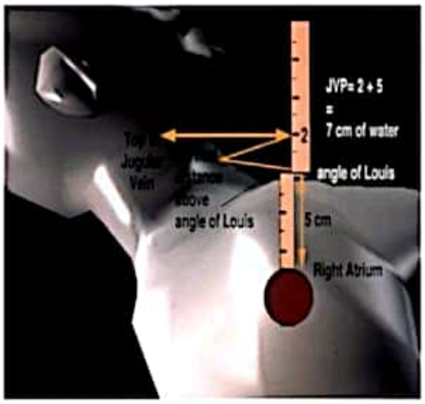
- Tamponade without pulsus paradoxus:
  - → LV dysfunction
  - → ASD
  - → AR
  - → Aortic dissection

Active space

JUGULAR VENOUS PRESSURE (JVP)

Introduction 00:01:12


Carotid Sinus
Common Carotid Artery
Internal Jugular Vein
Anterior Jugular Vein
External Jugular Vein
Innominate Vein
Superior Vena Cava


JVP= 2 + 5
=
7 cm of water
2
angle of Louis
Top Jugular Vein
Distance above angle of Louis
5 cm
Right Atrium

- Internal jugular vein used [EJV is superficial to SCM ; IJV is deep to SCM]
- Ⓝ JVP = 5 + 2 = 7 cm of H_2O
- JVP reflects ;
  - → Right atrial pressure
  - → Venous tone
  - → Volume of blood in venous system
  - → Right heart hemodynamics .
- IJV preferred because
  - → No valves
  - → Straight line course
  - → No extrinsic compressions
- IJV v/s carotid :- In IJV ;
  - → Superficial and lateral in neck
  - → Better seen
  - → 2 peaks
  - → Descents are more obvious
  - → Digital compression abolishes venous pulse
  - → Falls with inspiration
  - → Abdominal compression elevates JVP

Active space

Position of the patient: JVP measurement 00:08:27

- Patient's trunk inclined at an angle of 45° to bed → to Visualize upper level of venous column better
- 2 Scale method used :- Ⓝ JVP doesn't exceed 3-4 cm above the sternal angle

Since RA is approximately 5 cm below sternal angle, JVP → 9 cm H_2O = 7 mmHg

Elevated JVP: JVP of > 4 cm above sternal angle

- Waveforms best seen in ; Supine position , but upper level of venous Column not seen .

JVP elevation 00:11:53

- RV inflow impedence :- Tricuspid stenosis
  - Tricuspid myxoma
  - Constrictive pericarditis

- ↑ RV Pressure :- RV infarction
  - RVF
  - Pulmonary HTN
  - RVH
  - Pulmonary stenosis

- Circulatory overload :- Renal failure
  - Cirrhosis of liver
  - Excessive fluid administration
- SVC obstruction

Kussmaul sign and Abdomino jugular reflux 00:14:15

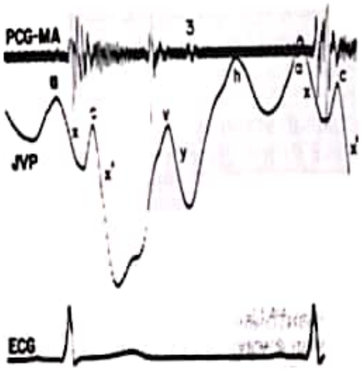
- Kussmaul's sign :- ↑ JVP during inspiration
  - Seen in ; Constrictive pericarditis
    Severe RHF
    RV Infarction
    RCM
    Impaired RV compliance

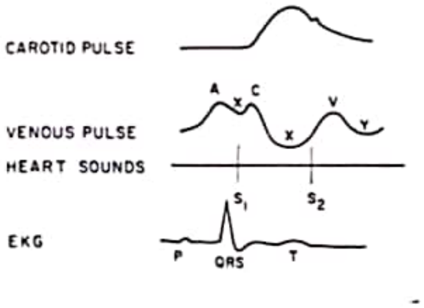
- Abdominojugular reflux :- A/K/a hepatojugular reflux
  - → Apply firm pressure to periumbilical region for 10 – 15 sec
  - → JVP remains elevated > 3cm for atleast 15 sec after resumption of spontaneous respiration [normally it rises transiently to < 1 cm]
  - → Positive AJR seen in ;
    - → Impending RHF
    - → TR
    - → COPD
    - → ↑ Sympathetic tone
- Reverse pulsus paradoxus : – SBP ↑ with respiration
  - Seen in positive pressure ventilation

Active space

Normal JVP waveforms

00:20:10





- a wave :
  - Because of atrial systole (effective RA contractions)
  - Pre - systolic wave ; dominant positive wave
  - Precedes S_1 ; follows ' P ' wave in ECG
- x descent :
  - During ventricular systole (due to atrial relaxation)
  - Larger than y descent
  - Ends just before S_2 → more prominent during inspiration
- C wave :
  - Systolic wave ; not usually visible on x descent
  - 2 Causes
    - upward bulge of closed TV , in IVC
    - Transmitted carotid artery pulsations
- x' descent :
  - Due to fall in right atrial pressure during early RV Systole
  - Systolic trough after C wave
  - Downward pulling of TV by contracting ventricle
- V wave :
  - Begins in late systole and ends in early diastole
  - Corresponds to S_2
  - Rise in RA pressure due to continued RA Filling during Ventricular Systole when TV closed .
- y descent :
  - Diastolic collapse wave → Beings and ends during diastole , well after S_2
  - Decline of RA pressure due to RA emptying during early diastole ; when TV opens
  - Early rapid filling phase.
- h wave :
  - Hirschfelder : discovered most of the wave forms
  - Small , brief positive wave following y descent
  - Usually seen when , diastole is prolonged and HR is slow

Abnormalities of waves

- a wave :-

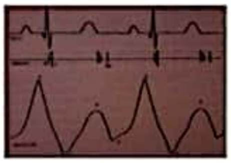
→ Large / prominent a wave : - ↑ RA contraction against resistance

↙ ↓

RA inflow obstruction → TS, TV myxoma

↓ ventricular compliance → RVH, PHTN, RCM, PS, RV infarction

Large a wave



→ Cannon a wave :- RA contracts against a closed TV during RV systole.

↙ ↘

Regular → Junctional rhythm, isorhythmic AV dissociation

Irregular → Complete heart block, VT, Ventricular pacing

→ Absent a wave : - No effective atrial contraction as in atrial fibrillation

- x descent :-

→ Prominent x descent :- Cardiac tamponade > constrictive pericarditis

→ Reduced x descent :- Atria failing to relax, ventricle unable to contract.

- RVF, RV infarction, atrial fibrillation, severe TR.

- y descent :-

→ Rapid y descent :- Constrictive pericarditis [Friedreich's sign], severe TR, RVF, ASD with MR

→ Slow y descent :- RA emptying and RV filling impaired

- TS, right atrial tumor, cardiac tamponade

[y descent may even be absent in tamponade]

- v wave :-

→ Prominent / Giant v wave / CV wave :- In severe TR

- Can sometimes cause head bobbing with each

[redacted]ver pulsations, pulsatile exophthalmos.

PERICARDIUM

23

Pericardium 00:01:05

- Parietal layer : Outer; From Somatopleuric mesoderm
- Pericardial cavity : In-between 2 layers
- Visceral layer : Inner; From Splanchnopleuric mesoderm

[Transmural filling pressure = Intracavitatory pressure – Intra pericardial pressure]

∴ Problem with → Venous return, → Filling of ventricles } → Diastolic issue → ↓EDV → ↓CO, ↑ESV

Acute pericarditis 00:04:24

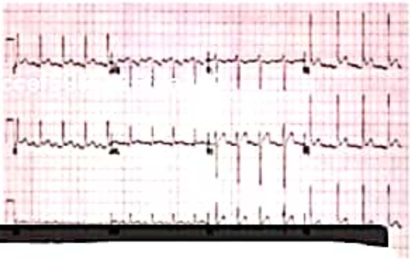
Differential diagnosis for chest pain → intense pleuritic pain varying with respiration, relieved on sitting and leaning forward

- Causes:

- MCC: Idiopathic > Post – viral [Coxsackie virus→MC]
- Others:
  - HIV; TB
  - Uremia (needs intensive and heparin – free hemodialysis)
  - Drugs: Procainamide, hydralazine, minoxidil
  - Autoimmune: Sjogren's syndrome
  - Tumor: Small cell lung cancer, Ca breast [mostly metastasis related]
  - Post – traumatic; Post – MI
  - IgG_4 associated disease

Acute pericarditis - diagnosis and management 00:12:04

ECG:
- → Global ST elevation with no reciprocal change
- → Concave upward ST elevation
- → PR segment depression
- → Diffuse T w[redacted] follows



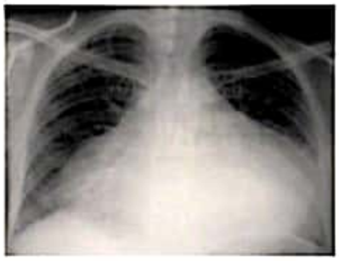
- Widespread ST elevation and PR depression
- Reciprocal ST depression and PR elevation in V1 and aVR

Pericardial friction rub:

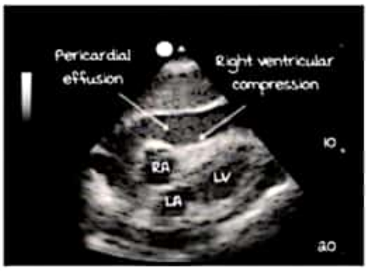
- Superficial; Scratchy/ leathery sound
- Can be seen without effusion also
- Best auscultated
  - → Leaning forward
  - → Diaphragm of stethoscope
  - → Forced expiration
- Very high – pitched sound
- Heard best towards left sternal border

- To rule out pericardial effusion;

→ X-ray : - Cardiac borders lost
  - 'Water bottle appearance'



→ ECHO :



- High – risk patient:
  - Fever and sub-acute course
  - Cardiac tamponade
  - Large pericardial effusion
  - Elevated trop I → suggests myopericarditis
  - On anti-coagulants

- management:
  - DOC: NSAIDS
  - Steroids not routinely recommended ∵ ↑ relapse risk
  - 60% with acute pericarditis will have effusion, 90% of which will be mild
  - Ewart's sign: Dullness along inferior border of left scapula in Large pericardial effusion

Chronic constrictive pericarditis 00:23:09

- obliteration of pericardial cavity by granulation tissue → contracts and forms scar → calcification

  ∴ Rigid, calcified, inelastic pericardial cavity ----> unable to transmit the negative intra – thoracic pressure to the heart during inspiration
- impaired diastolic filling due to rigid pericardium → max filling during first 1/3rd of diastole → stops abruptly → therefore deep accentuated y-descent
- during systole → normal ventricular filling → normal/mildly accentuated x-descent
- Pulsus paradoxus in 1/3rd of patients [∵ ventricular inter – dependence]
- ventricular pressure graph plotting ⟶ "Square root sign"
- Kussmaul's sign: Rise in JVP with inspiration
- Equalization of pressure in all 4 chambers
- Pericardial calcification, Scarring; etc
- 'Pericardial Knock' may be present

Causes for chronic constrictive pericarditis 00:40:40

- MCC: Tuberculosis
- Others:
  - Relapsing viral pericarditis
  - Connective tissue disorders → Sjogren's syndrome
    → IgG_4 disease
  - Histoplasmosis
  - malignancy → Rhabdomyosarcoma
    → metastasis ⟶ Small Cell Lung Cancer [SCLC]
  - Radiation

- Features:
  - Chronically ill patient with wasting and cachexia
  - Ascites hepatomegaly, pedal edema
  - Broadbent sign: Retraction of apex during systole
  - Early diastolic 'Pericardial Knock'
  - Heart size Ⓝ
- Differentials: Cor pulmonale; Chronic liver disease; Restrictive Cardiomyopathy [RCM]
- Diagnosis:
  - ECG: low voltage QRS complexes and diffuse T– wave Flattening
  - IOC: MRI
- Treatment: pericardial resection is definitive → Should be done as early as possible

Constrictive pericarditis v/s RCM

00:51:24

Constrictive Pericarditis	Restrictive cardiomyopathy
• Pericardial knock (+)	(–)
• S_3 (–)	(+)
• Exaggerated respiratory variation in flow velocity (++)	(–)
• Kussmaul's sign (+++)	(+)
• Pulsus paradoxus ($1/3^{rd}$)	(+/–)
• Equalization of diastolic Pressures (++)	(–)
• Pericardial thickening, Calcification (++)	(–)
• RV size Ⓝ	Ⓝ
• x–descent (mild prominent)	(Prominent)
• y–descent (very prominent)	(Just present)

Cardiac tamponade

00:57:07

- Accumulation of fluid in pericardial space significant enough to cause serious obstruction to inflow of blood

  ∴ Diastolic compliance reduces
  → much severely reduced
  → Heart reduces in size
  → CO ↓↓ → Hypotension

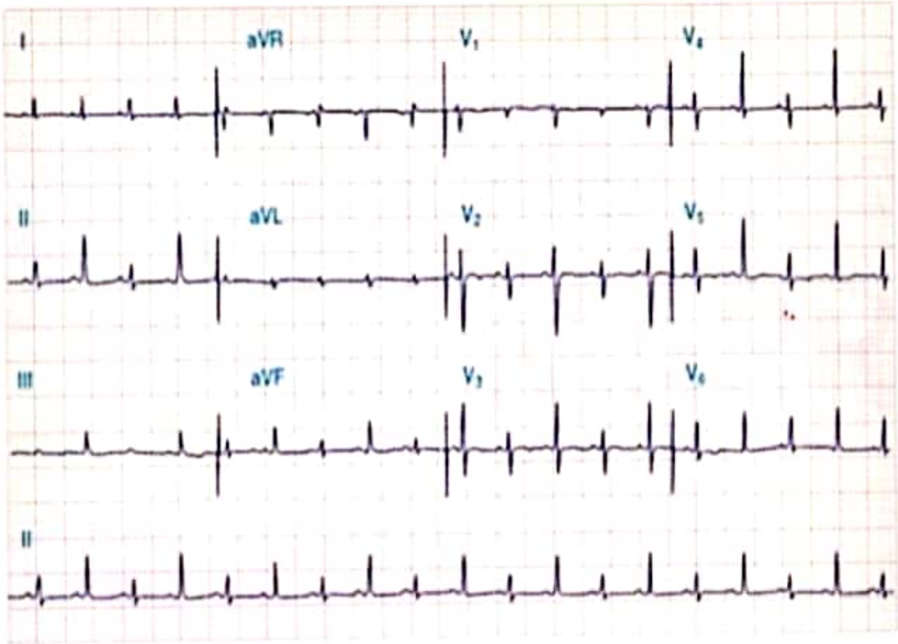
- Venous return only during systole
  → Prominent x-descent
  → No y-descent

- Respiratory variation (++) → Right side filled during inspiration and left side filled during expiration

  ⇒ Systolic BP ↓↓↓ → "Pulsus paradoxus"

- [Beck's triad: Hypotension (↓CO) + muffled heart sounds + elevated JVP]

- ECG: electrical alternans: alternating complexes of different amplitudes



Electrical alternans. this tracing was obtained from a patient with large pericardial effusion with tamponade
firvis AL Goldberger: Electrocardiography, in RO Bonow et al (eds): Braunwald's heart disease, 9th ed, philadelphia elsevier.

Active space

- Treatment: "Emergency subxiphoid Pericardiocentesis"

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	Cardiac tamponade	Constrictive pericarditis	Restrictive cardiomyopathy
Pulsus paradoxus	+++	1/3	+++
x descent	+++	Nomal or mid	+++
Y descent	Absent	+++	+++
Kussmaul sign	–	+++	+
Pericardial knock	–	+++	+
S3	–	–	+
Electrical alternans	+	–	–
Thickened & calcified pericardium	–	+	–
Respiratory variation in flow velocity	+	+	–

FIRST HEART SOUND (S_1)

Terminology

00:03:32

- Intensity (objective) = Loudness (subjective)
- Frequency (objective) = Pitch (subjective)
- Sounds:
  - → High frequency:
    - Soft blowing or musical
    - ausculated over wide area
    - Thrills uncommon
    - better heard with diaphragm of stethoscope
    - Considerable pressure difference between 2 chambers
  - → Low frequency:
    - Rough, rumbling, dull
    - Not over wide area
    - Palpable thrill ⊕
    - Bell of stethoscope
    - Associated with ↑ amplitude
    - Pressure difference between chambers is less
  - → mixed frequency:
    - Harsh quality sounds
    - High frequency + low frequency
    - Aortic stenosis murmur
      - → High pitched component
        - → Radiated to apex
      - → Low pitched component
        - → Best heard in aortic area

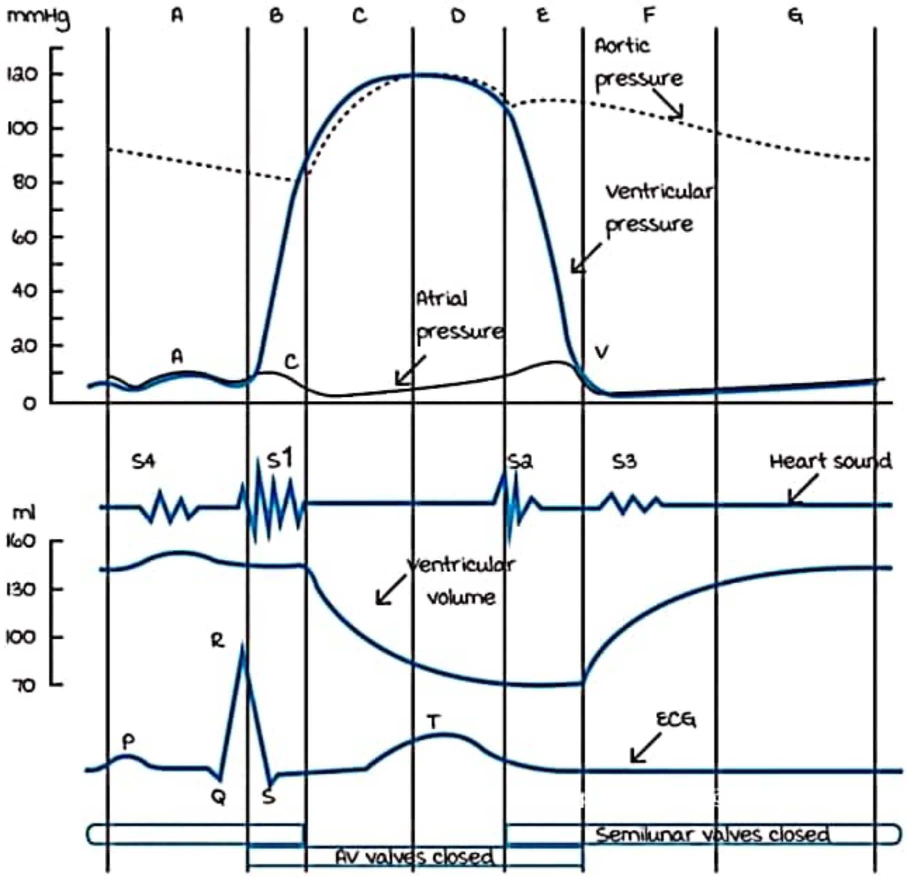
- All heart sounds are high pitched except → S_3, S_4, S_4 Tumor plop (all diastolic sounds)
- All murmurs are high [redacted]
Tricuspid stenosis murm[redacted]
→ mid diastolic murmur)

- order of diastolic sounds : -(mnemonic) "OP Time 3-4"
  ↓

  Opening snap → pericardial Knock → tumor plop → S_3 → S_4
  (S3 & S4- late diastolic sounds)

First heart sound: S_1 00:16:09

- Atrial systole is the last part of ventricular diastole
- when the ventricles are fully filled with blood, ventricular pressure exceeds atrial pressure.
- Atrial systole → Isovolumetric contraction (IVC)
  ↓
  mitral valve and tricuspid valve have to close → causing S_1


mmHg
A
B
C
D
E
F
G
120
100
80
60
40
20
0
Aortic pressure
Ventricular pressure
Atrial pressure
A
C
V
S4
S1
S2
S3
Heart sound
ml
160
130
100
70
Ventricular volume
R
P
Q
S
T
ECG
Semilunar valves closed
AV valves closed

- mv leaflets:
  - Peripheral smooth zone
  - Central rough zone / coaptation zone

- Zone of coaptation: A conical zone formed when MV leaflets come together

↓

Final "sudden tensing of leaflets"
Responsible for heart sound S I

- 'S_1' is always a high-pitched sound → M_1, T_1 } Seperated by <20 milli seconds

Ventricular systole -3 phases	Ventricular diastole -5 phases
1) IVC (Isovolumetric contractions).	1)PR (Protodiastole)
2) Rapid ejection	2)IVR (Isovolumetric Relaxation)
3) Reduced ejection	3)Rapid filling
	4)Reduced filling
	5)Atrial systole

Factors affecting S_1

00:27:31

I) Structural integrity of valve:
→ Loss of leaflet tissue (IE) → Soft S_1
→ Inadequate coaptation (MR) → Soft S_1

- Moderate – Severe MS: - ↑ left atrail pressure → mobile portions of valve leaflet to be widely seperated → delayed valve closure → loud S_1

- Calcified / degenerated mitral valve (long standing MS) : Immobilizes leaflet → soft S_1

II) Velocity of valve closure: Position of MV at the onset of systole

- PR interval: from atria to upper part of bundle of His.
  - Short → Left ventricular pressure ↑ very quickly → mitral valve leaflets are farther apart . closes with high velocity large excursion → Loud S_1
  - Long → Longer diastolic filling time → LV pressure gradually ↑ → mitral valve leaflet slowly drifts together → Lesser distance between leaflets → Soft S_1

III) Premature AV valve

- Soft S_1 ⊕ closure:
- LV pressure exceeds LA pressure even before onset of systole
- In AR, chronic AR + LV dysfunction

IV) Velocity of contraction: $\frac{dP}{dt}$ of isovolumetric contraction

- [↓↓] → Soft S_1
  - MI [especially acute coronary syndrome of LAD]
  - myocarditis
  - MR
  - Ventricular septal defects
- [↑↑] → loud S_1
  - Beri beri
  - Thyrotoxicosis
  - Exercise
  - Anemia

  } High output states

V) Heart rate: Tachycardia → short PR interval → reduced diastole time → widely opened valves → loud S_1

VI) Transmission characteristics of thoracic cavity and chest wall:

- Obesity, emphysema and pericardial effusion → ↓ intensity of auscultatory events
- Thin chest wall → ↑ intensity

Loud T_1, M_1-T_1 split, variable S_1 00:43:21

- Loud T_1: → TS, TV tumor (myxoma), ASD, TAPVC (Total anomalous pulmonary venous connection)

Loud S1 in MS:-

-Open mitral valve at the onset of diastole.

-Delayed closure.

-High LV pressure required to close.

-Thickened but mobile leaflets.

Soft S1 in MR:-

- dp/dt of IVC reduce.
- Loss of coaptation.
- Shortening of leaflets.

- M_1-T_1 split:

→ Left bundle branch block → Delay in LV contraction → Delayed M_1
→ T_1 can occur Before M_1 → "Reversed split of S_1"

→ Right bundle branch block → M_1 occurs on time
→ Delayed T_1 → "Wide split S_1"

- Variable S_1:
  - → Atrial fibrillation:
    - → Short cycles → Loud S_1
    - → Long cycle → Soft S_1
  - → Ventricular tachycardia
  - → Complete heart block
  - → Atrial flutter with varying conduction

Variable S1 seen in VT (Differentiates from SVT with aberrancy)

- Acute MI:
  - → Delayed contraction → Soft S_1
  - → $\downarrow \frac{dp}{dt}$ → Soft S_1
  - → Associated with MR → Soft S_1
  - → Associated with LBBB → "Reversed split of S_1"

SECOND HEART SOUND

S_2 00:00:09

- High frequency → 120-150 Hz
- Closure of aortic valve (AV) and pulmonary valve (PV) sets entire cardio-hemic system into vibrations
- Towards end of reduced ejection phase [when aortic pressure exceeds LV pressure]
- Difference between
  A_2 and P_2 → 30 ms → Expiration
  → 40-50 ms → Inspiration → A_2-P_2 split ⊕
- A_2 is louder [∵ higher pressure in aorta]
- A_2-P_2 widening best appreciated during inspiration [∵ ↑venous return to Ⓡ side]

Hangout interval 00:05:15

- Time interval from cross-over pressure (expected closure of semi lunar valves) to actual closure of the valves is called 'Hangout interval'
- Depends on → Pressure difference between chamber and vessel
  → Distensibility of the arterial system

⇒↑ pressure difference and
less distensibility → shorter hangout interval

In aorta (A_2) = 30 ms
pulmonary artery (P_2) = 80 ms } ∴ A_2 occurs before P_2

Factors affecting A_2/P_2 intensity 00:09:21

→ Pulmonary area auscultated for A_2-P_2 split → Normally, A_2 is louder than P_2

→ Loud P2 ---- P2 as loud as A2 in pulmonary area

- Factors:
- Pressure beyond valve ie
    - → SHTN systemic HTN → Loud A_2
    - → PHTN pulmonary hypertension → Loud P_2
    - } Loud S_2
- Flow across the valve ↑ → Loud S_2
- Dilatation of vessel wall beyond valve → Loud S_2
    - → Idiopathic dilatation of pulmonary artery [P_2]
    - → Aortic root dilatation due to marfan's, syphilis, ankylosing spondylitis → can produce AR [A_2]
- AR due to aortic root dilatation → Loud A_2

  AR due to degenerative disease → Soft A_2
- PHTN with intact RV function → Loud S_2 [A_2, P_2 equally loud]

  moderate- severe PHTN → Loud S_2 [Only loud P_2 ∵ masking]

  Severe PHTN with RVF → Wide split S2 with loud P_2
- TGA → Aorta arises more anteriorly → Loud A_2

  ASD → Dilated pulmonary trunk, ↑ flow across valve → Loud P_2
- valvular AS
  valvular AR
  valvular PS
  } degeneration → Soft / diminished A_2/P_2

Warning : Not all points are covered in the notes, especially conceptual explanations. Please use the notes in conjunction with Marrow Edition 4 videos.

Single S_2, wide split S_2, reversed split S_2 00:18:22

- Single S_2:
    - MC : Aging
    - Atresia of semilunar valve
    - Severe AS/PS
    - TGA [loud A_2, absent P_2]
    - PAH moderate-severe)

      ↓
    - Continuation of PAH

- Wide split S_2: Split heard during expiration/standing position
  - → Wide variable physiological split:-
    - Delayed P_2:
      - Electrical delay (RBBB or LV pacing)
      - PS
      - ASD
      - PHTN + RVF
      - Pulmonary embolism
    - Early A_2:
      - severe MR
      - VSD
  - → Wide fixed physiological split:- If a component fail to move with respiration

    ↓
    - → When RV/LV stroke volume fails to change with respiration → RVF
    - → Simultaneous ↑ in both RV and LV filling → ASD
- Reversed split / paradoxical split S_2:
  - P_2 occurs before A_2
  - Inaudible split during inspiration but audible in expiration
    - → Early P_2:
      - TR
      - WPW type B
    - → Delayed A_2:
      - Electrical delay (LBBB or RV pacing)
      - LVH (AS / HOCM)
- Massive pulmonary embolism:
  - → Wide split
  - → With RHF → Wide 'fixed' split

THIRD AND FOURTH HEART SOUNDS , EJECTION CLICKS AND OPENING SNAP

37

Third heart sound: S_3

00:00:12

- A/K/a Ventricular gallop
- Low pitched diastolic sound
- Late in diastole [predominantly in rapid filling phase]
- Theories:
  - Impact theory: Ventricle resisting rapid inflow → Vibrations
  - Ventricular theory: Sudden cessation of ventricular filling
  - Valvular theory: Sudden limitation of LV expansion
- Cause:
  - Ⓝ Ventricle with excess,
    rapid inflow → Children, young adults
    → Hyperkinetic states
  - Less than Ⓝ filling of ventricle with ↓ compliance → Diastolic overload State → MR, VSD, PDA; [S_3 rare in AR ; S_3 ⊕ in AR with LVF]
  - Overfilled ventricle with ↑ ESV → LV systolic dysfunction
    → AV valve stenosis ie; MS/TS → S_3 is NOT possible
- S_3 follows A_2 by 120-160 milli sec
- Gallop rhythm:
  Auscultatory phenomenon of tripling [S1, S2, S3] or Quadrupling [S1, S2, S3,S4] of heart sounds (resembles the canter of a horse)
- Normal S_3 → Disappear in upright position
- Abnormal S_3 → Better heard after isotonic exercise, passive leg raising
- LVS_3: Best heard with bell of stethoscope, at apex, on expiration, in Ⓛ lateral position, ↑ with isometric hand grip; LVF features ⊕

  RVS_3: At left lower sternal border, on inspiration, in supine position, No change with isometric hand grip; Elevated JVP ⊕

- MR and S_3 not used for prognosis; Heart failure and S_3 → Bad prognosis

- Heart failure without S_3: → MS; TS; Pericardial tamponade
- D/D for S_3:
  - Pericardial Knock
    - → Loss of pericardial elasticity
    - → High pitched, sharper
    - → Occurs earlier
    - → Louder with inspiration and squatting [∵ ↑venous return]

Fourth heart sound : S_4

00:17:30

- A/K/a atrial gallop / Pre-systolic gallop
- In late diastole [atrial systole phase] ; Low pitched (20-30 Hz)
- Abnormally turbulent flow due to healthy normal atria contracting Vigorously to pump blood into non – compliant hypertrophic or fibrotic but non – dilated LV Cause S_4
- Pre requisites:
  - → Healthy atria in sinus rhythm
  - → Non-stenoic AV valves
  - → Non-compliant, non-dilated ventricle
  - → LVEDP > 15 mmHg
  - → Restriction to filling (RCM, HOCM, RVH, amyloidosis)

S_4
- → Present → Acute MR (due to hyperdynamic atrial systole)
- → Absent → Chronic MR (due to poor LA contractility)

- Significance of S_4:
  - Universally present in patients with STEMI
  - Presence indicate infarction of atleast 7-10% of myocardium
  - Absent in atrial fibrillation / atrial infarction
  - S_4 is a reflection of well maintained systolic function & impaired diastolic function (Impaired systolic function = S3)
- S_4 – Severe AS; S_4 does not correlate severity of HOCM

Ejection clicks 00:26:51

- Are systolic: Produced by opening of semilunar valves
  - → Valvular EC : Abrupt halting of a doming valve at the onset of LV systole → AS/PS → Loud S_2 if EC associated
  - → Vascular EC : Sudden distension of vessel beyond the valve → Dilation of vessel or systemic HTN / pulmonary HTN → Diminished S_2 if EC associated
- Common in bicuspid aortic valve
- Extremely severe stenosis, calcification, degeneration of AV/PV → EC unlikely
- PS: EC is common in valvular PS, better heard in expiration
- AS with EC ≃ Loud S_1
  - → Better heard at apex → Loud S_1 likely
  - → Better heard at base /Ⓛlower sternal border → EC likely

Non – ejection sounds 00:32:11

- By MVP [mitral valve prolapse] /TVP: Systolic sounds

  ↓

  By 'myxomatous degeneration of valve'
- Caused by tension in AV valves during systole
- Systolic regurgitant murmur

  [Cooing dove murmur] = Non-ejection sounds

  ↓

  Increase with standing and Valsalva

Opening snap (OS) 00:34:31

- High pitched, diastolic sound; 60-100 milli sec after S_2; In 'Isovolumetric relaxation phase'
- OS = mitral stenosis
- Pre requisites:
  - → ↑ LA PRESSURE
  - → Thickening of valve
  - → Doming motion of valve leaflet towards LV

- S_2 – OS Interval : Severity of MS is inversely proportional to LA pressure

  ⇒↓ S_2 – OS internal →↑LA pressure – Severe MS

- mild MS → S_2 – OS interval >120ms → LAP <5 mmHg

  moderate MS → 60-80 ms → 5-10 mmHg

  Severe MS → 40-60 ms → >15 mmHg

- OS absent in MS
  - → Calcified valve
  - → Severe AR/MR with MS
  - → CAD with LV dysfunction

- ↑ HR → S_2 – OS / A_2 – OS interval [↓↓]

  HTN → [↑↑]

  LVEDP → [↑↑]

- OS in non – stenotic valve: → MR, VSD, TR, ASD, Ebstein anomaly

Tumor plop

00:42:26

- Low frequency; Heard after OS
- In myxoma [Ⓡ/Ⓛ atrial orifice]; Due to abrupt halting of filling during diastole
- LA myxomas are more common

HYPERTENSION: BASICS, RECENT GUIDELINES, PATHOGENESIS AND CONSEQUENCES

Blood pressure 00:01:30

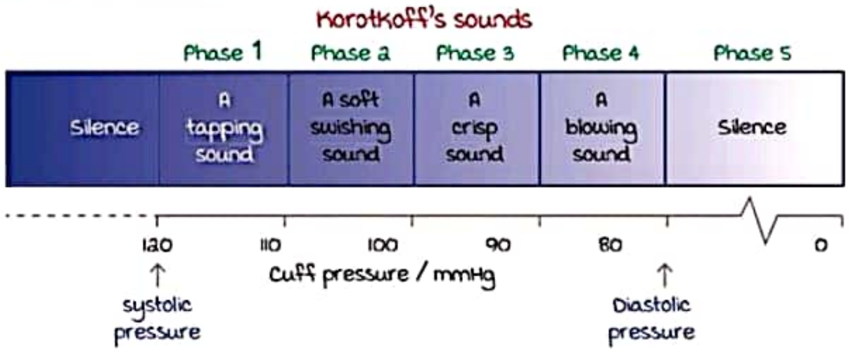
- European society of hypertension (ESH) 2018
- Lateral pressure exerted by the column of blood on the vessel wall measured in mmHg
- Blood pressure = Cardiac output × Peripheral vascular resistance (PVR) = (Stroke volume × Heart rate(HR)) × PVR = {(End diastolic volume−End systolic volume) × HR} × PVR

⇒ BP is determined by
- → Pre-load (EDV):- Volume of blood in ventricle at end of diastole
- → Afterload (PVR):- Resistance against which ventricle has to pump blood
- → myocardial contractility
- → Venous return

→ 'Systolic failure' mostly refers to left heart (LV)
→ 'Diastolic failure' to right heart (RV)

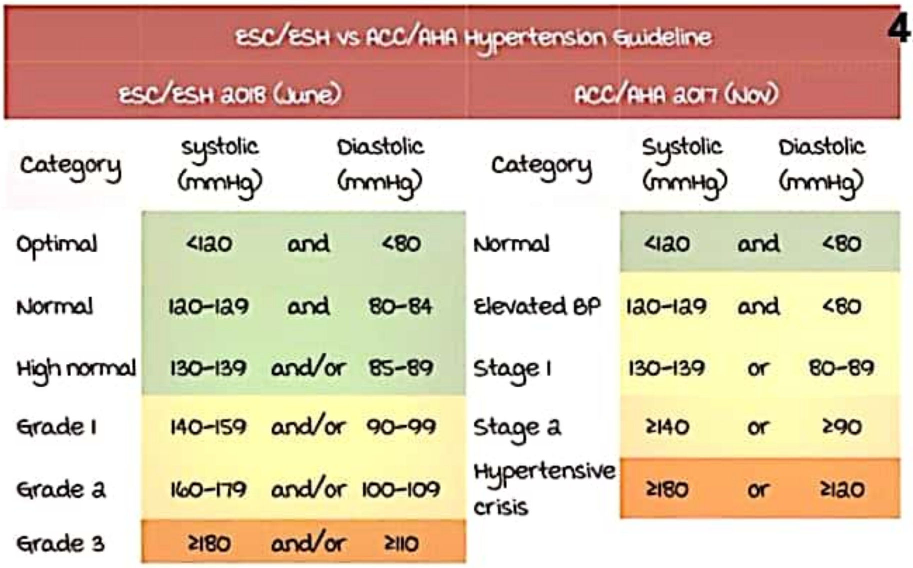
Techniques to measure BP 00:09:01

- Best method: 'Oscillometric method' using 'OMRON 907 oscillometric BP apparatus' (sprint trial)
- 24-hr ambulatory BP monitoring (recommended)
- Palpatory method, Auscultatory method, Aneroid sphygmomanometer
- Korotkoff sounds:


Korotkoff's sounds
Phase 1
Phase 2
Phase 3
Phase 4
Phase 5
Silence
A tapping sound
A soft swishing sound
A crisp sound
A blowing sound
Silence
120
110
100
90
80
0
Cuff pressure / mmHg
systolic pressure
Diastolic pressure

- Auscultatory gap:
  - commonly seen in HTN,
  - Disturbance of flow of blood in arm
  - Overestimates DBP

Guidelines 00:19:01



ESC/ESH vs ACC/AHA Hypertension Guideline							
ESC/ESH 2018 (June)				ACC/AHA 2017 (Nov)			
Category	systolic (mmHg)		Diastolic (mmHg)	Category	Systolic (mmHg)		Diastolic (mmHg)
Optimal	<120	and	<80	Normal	<120	and	<80
Normal	120-129	and	80-84	Elevated BP	120-129	and	<80
High normal	130-139	and/or	85-89	Stage 1	130-139	or	80-89
Grade 1	140-159	and/or	90-99	Stage 2	≥140	or	≥90
Grade 2	160-179	and/or	100-109	Hypertensive crisis	≥180	or	≥120
Grade 3	≥180	and/or	≥110				

Factors leading to HTN 00:22:07

→ Primary / Essential HTN:- 90-95%
→ Secondary HTN:- 5-10%

- Primary/ essential HTN:

→ Environmental factors

→ Strong contributing factors:
- most important : Obesity [weight gain] → Strongest, independent risk factor
- Diet high in Na^+, Diet low in K^+, Ca^{2+}, mg^{2+}
- Stress

→ Possible contributing factors:
- Alcohol consumption
- Low vitamin D
- High fructose diet
- Lack of exercise

→ Genetic factors:

- Either parent having HTN: 10-15%
- Both parents having HTN: 30-40%
- Gene: "α - adducin gene"

Pathogenesis:

00:26:39

Genetic + environmental factors

→ Volume related HTN: - $Na^+ + H_2O$ ↑↑↑ intra-vascularly

- Pressure natriuresis:- Even if CO↑, as long as kidneys is normal, it is not possible to have sustained rise in BP
- ↑CO → ↑renal blood flow(RBF) → ↑ renal medullary flow

  ↓

  ↑ Renal interstitial hydrostatic pressure

  ↓

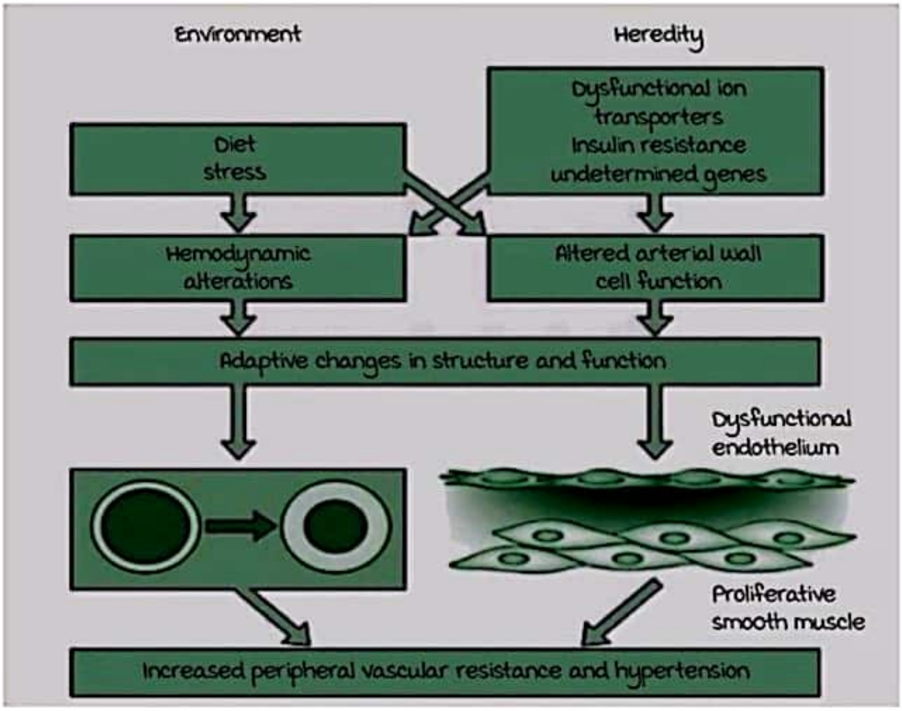
  Na^+ & H_2O excretion

- the only condition which is volume dependent- Chronic kidney disease(CKD)/ end stage renal disease
- 80%-Volume dependent, 20% pressure dependent]

→ Pressure related HTN: - Sympathetic overactivity or Renin angiotensin system(RAS)

- Functional vasoconstriction, Defect in smooth muscle (s.m) growth
- ↑ PVR → HTN

S.m proliferation
dysfunctional endothelium } → ↑ PVR → HTN


Environment
Heredity
Dysfunctional ion transporters
Insulin resistance
undetermined genes
Diet
stress
Hemodynamic alterations
Altered arterial wall cell function
Adaptive changes in structure and function
Dysfunctional endothelium
Proliferative smooth muscle
Increased peripheral vascular resistance and hypertension

Active space

Pathogenesis of benign HTN 00:36:05

- ↑ BP → further endothelial damage → extra cellular matrix ↑ sm ↑

↓

Worsening of atherosclerosis ← "Hyaline arteriosclerosis" → Benign /essential/1°HTN

↓

Rupture, clotting of small vessel, occlusion $\xrightarrow{5\%}$ "malignant HTN"

- → Hyperplastic arteriosclerosis
- → Fibrinoid necrosis
- → Onion skin change

Sympathetic overactivity 00:41:12

- Sympathetic system → vasoconstriction(VC) → ischemic heart disease(IHD) → HTN → Target organ damage
- most important target organ damage → LVH (by sympathetic overactivity)
- Causes of sympathetic overactivity:
  - most important: Endothelial dysfunction [By-dyslipidemia, diabetes, obesity, smoking, oxidative stress.etc]
  - Renal ischemia (β_1 activating RAS)

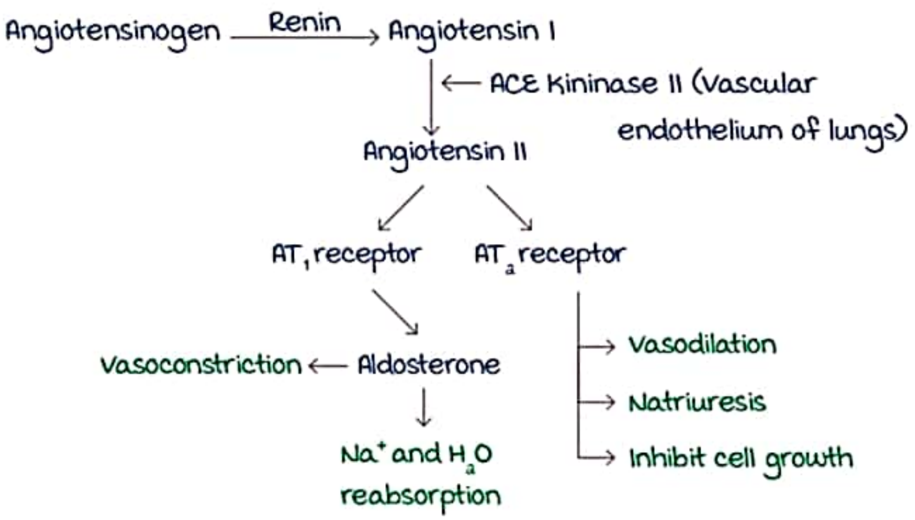
Renin angioyensin aldosterone system 00:45:43

- 3 stimuli for renin → Product by juxtaglomerular cells, β_1, ↓ renal perfusion pressure

↓

Human plasma has 5 times more pro-renin than renin

Renin produced by JG cells: they are granular cells in tunica media of afferent arterioles


Angiotensinogen
Renin
Angiotensin I
ACE Kininase II (Vascular endothelium of lungs)
Angiotensin II
AT_1 receptor
AT_2 receptor
Vasoconstriction
Aldosterone
Na^+ and H_2O reabsorption
Vasodilation
Natriuresis
Inhibit cell growth

⇒ Angiotensin II receptor blockers might be better than angiotensin- converting enzyme (ACE)inhibitor (∵ AT_2 spared)

Consequences of HTN

00:53:33

- Causes target organ damage
    - Heart: LVH → Diastolic dysfunction
    - Kidney: RAAS → Renal artery stenosis
    - Brain: Stroke; multiple lacunar infarcts
      (multi-infarct state associated with severe cognitive decline)
    - Peripheral occlusive disease: ABPI(ankle brachial pressure index)<0.9

HYPERTENSION: CLASSIFICATION, CONCEPTS AND MANAGEMENT

European Society of Hypertension (ESH)-2018

00:00:10

- Diagnosis of hypertension (HTN) should be made on the basis of 24-hour ambulatory BP
- If 24-hour ambulatory BP cannot be done then repeated office BP or repeated home BP measurements should be done (use oscillometric method)

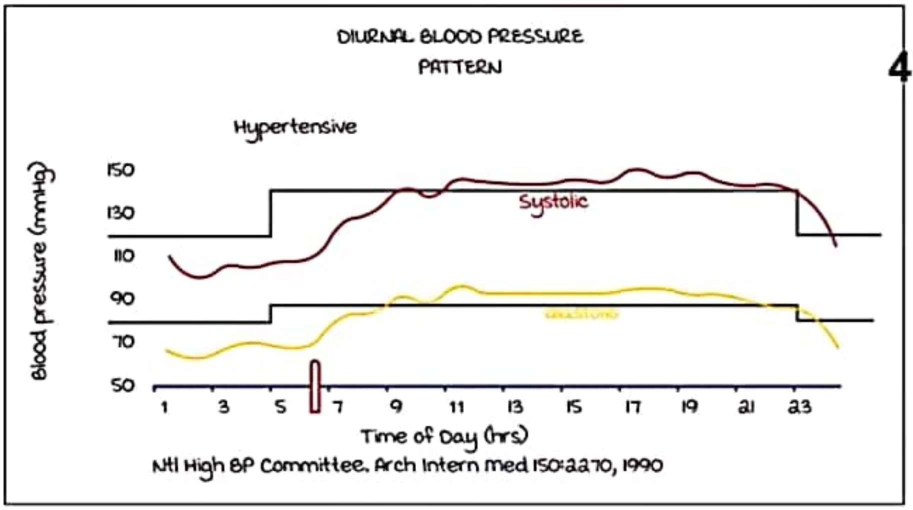
Definitions of hypertension according to office, ambulatory, and home blood pressure levels

Category	SBP (mmHg)		DBP (mmHg)
Office BP	≥140	and/or	≥90
Ambulatory BP			
Daytime (or awake) mean	≥135	and/or	≥85
Night-time (or asleep) mean	≥120	and/or	≥70
24 h mean	≥130	and/or	≥80
Home BP mean	≥135	and/or	≥85

BP = Blood Pressure; DBP = Diastolic Blood Pressure; SBP = Systolic Blood Pressure.

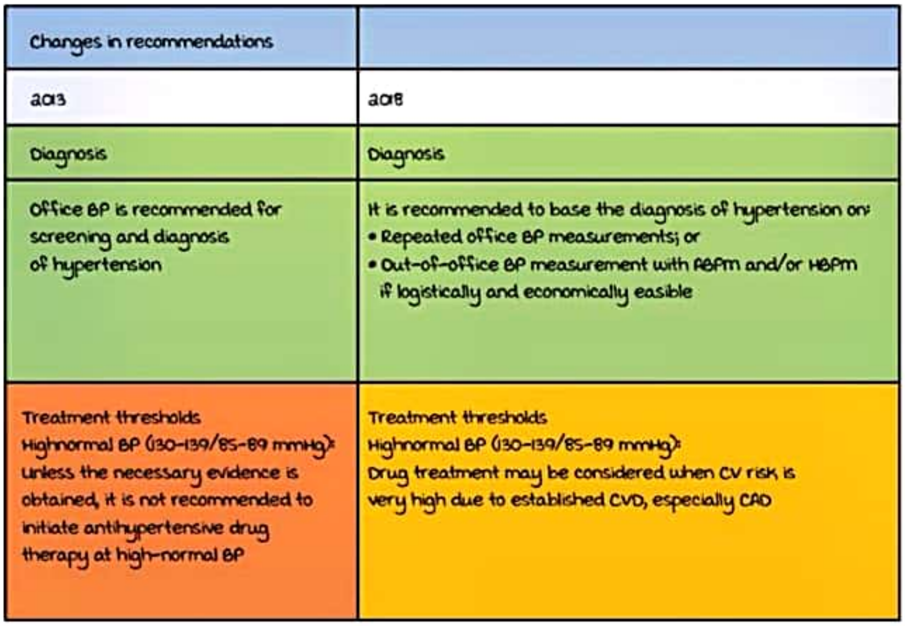
Refers to conventional office BP rather than unattended office BP

- ▸ The portable monitor is worn on a belt connected to a standard cuff on the upper arm
- ▸ When complete, the device is connected to a computer that prepares a report of the 24 hour, day time, night time, and sleep and awake (if recorded) average systolic and diastolic BP and heart rate



Ntl High BP Committee. Arch Intern med 150:2270, 1990

Changes in recommendations 00:04:45



Changes in recommendations	
2013	2018
Diagnosis	Diagnosis
Office BP is recommended for screening and diagnosis of hypertension	It is recommended to base the diagnosis of hypertension on: • Repeated office BP measurements; or • Out-of-office BP measurement with ABPM and/or HBPM if logistically and economically easible
Treatment thresholds Highnormal BP (130-139/85-89 mmHg): Unless the necessary evidence is obtained, it is not recommended to initiate antihypertensive drug therapy at high-normal BP	Treatment thresholds Highnormal BP (130-139/85-89 mmHg): Drug treatment may be considered when CV risk is very high due to established CVD, especially CAD

Advantages of 24-hour ambulatory BP monitoring 00:06:58

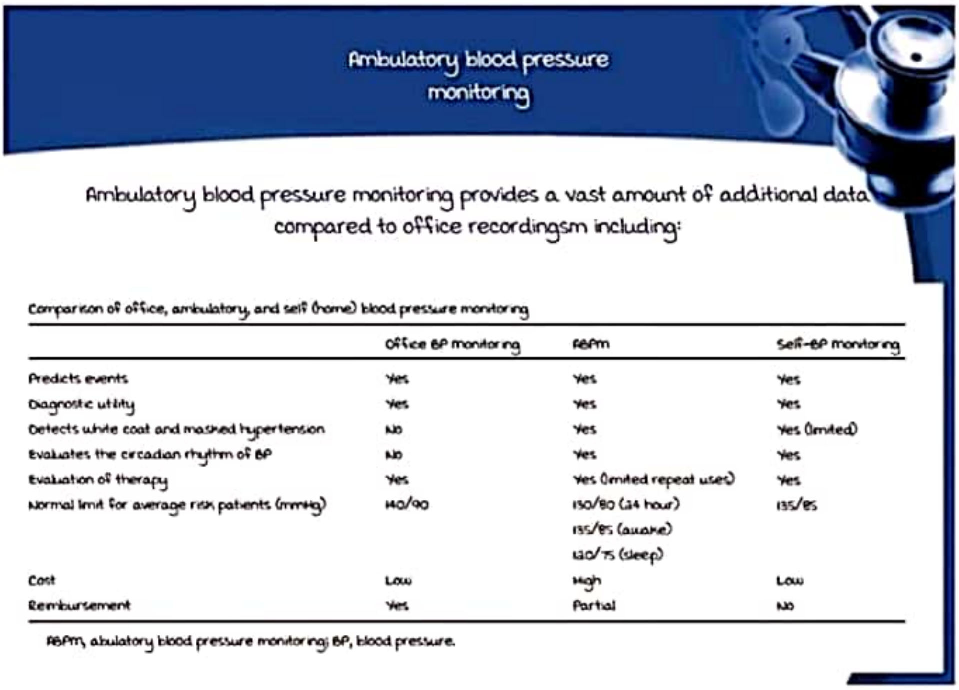
1. White coat hypertension can be diagnosed

2. To diagnose masked hypertension(reason for increased cardio-vascular morbidity & mortality)

3. Absence of nocturnal dipping is associated with ↑ cardiovascular mortality. Commonly seen in diabetic patient

4. Episodic hypertension } pheochromocytoma
5. Postural hypotension }

Active space



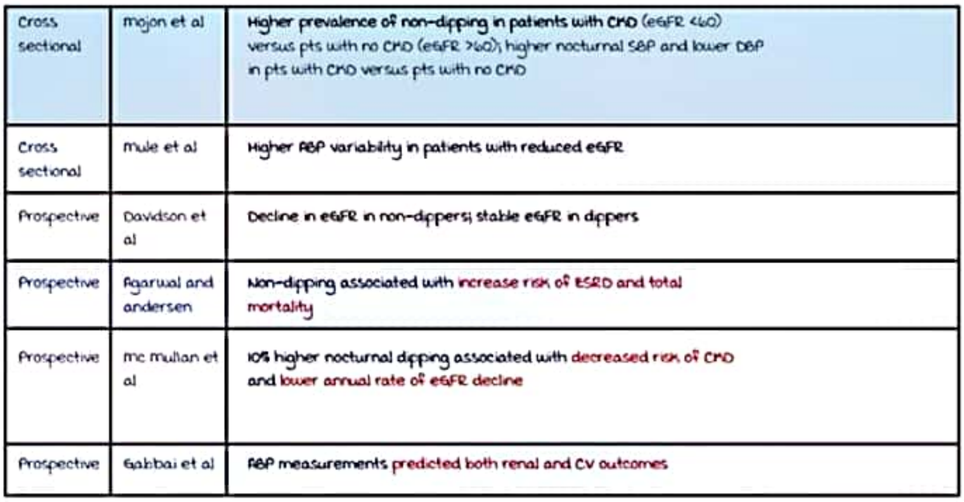
Ambulatory blood pressure monitoring

Ambulatory blood pressure monitoring provides a vast amount of additional data compared to office recordingsm including:

Comparison of office, ambulatory, and self (home) blood pressure monitoring

	Office BP monitoring	ABPM	Self-BP monitoring
Predicts events	Yes	Yes	Yes
Diagnostic utility	Yes	Yes	Yes
Detects white coat and masked hypertension	No	Yes	Yes (limited)
Evaluates the circadian rhythm of BP	No	Yes	Yes
Evaluation of therapy	Yes	Yes (limited repeat uses)	Yes
Normal limit for average risk patients (mmHg)	140/90	130/80 (24 hour) 135/85 (awake) 120/75 (sleep)	135/85
Cost	Low	High	Low
Reimbursement	Yes	Partial	No

ABPM, abulatory blood pressure monitoring; BP, blood pressure.



Cross sectional	mojon et al	Higher prevalence of non-dipping in patients with CKD (eGFR <60) versus pts with no CKD (eGFR >60); higher nocturnal SBP and lower DBP in pts with CKD versus pts with no CKD
Cross sectional	mule et al	Higher ABP variability in patients with reduced eGFR
Prospective	Davidson et al	Decline in eGFR in non-dippers; stable eGFR in dippers
Prospective	Agarwal and andersen	Non-dipping associated with increase risk of ESRD and total mortality
Prospective	mc mullan et al	10% higher nocturnal dipping associated with decreased risk of CKD and lower annual rate of eGFR decline
Prospective	Gabbai et al	ABP measurements predicted both renal and CV outcomes

Altered BP variability and ambulatory BP pattern in CKD patients

Secondary hypertension

00:11:33

- 5-10% are secondary hypertension
- Complications are more in secondary hypertension than in 1° HTN

Causes

1. Renal:

⇒ Renovascular causes (mc cause among renal causes)

  - Large vessel : Renal artery stenosis(RAS)
  - Small vessel : Thrombotic microangiopathy(TMA)

⇒ Renal parenchymal disease ⇒ Chronic glomerulonephritis (IgA Nephropathy)

II. Endocrine

- Conn's Syndrome
- Pheochromocytoma
- Primary hyperparathyroidism
- Cushings syndrome
- Hyperthyroidism

III. monogenic form of 2° HTN

- Liddle's Syndrome
- Apparent mineralocorticoid Excess (AME)
- Glucocorticoid Remediable Aldosteronism (GRA)
- Gordon Syndrome

IV. miscellaneous

- Obstructive sleep apnea syndrome(OSAS)
- Coarctation of aorta

Common causes of secondary hypertension

Cause	Prevalence in hypertensive patients	Suggestive symptoms and signs	Screening investigations
Obstructive sleep apnoea	5-10%	Snoring; Obesity (can be present in non-obese); morning headache; daytime somnolence	Epworth score and ambulatory polygraphy
Renal parenchymal disease	2-10%	mostly asymptomatic; Diabetes; Haematuria, proteinuria, nocturia, anaemia, renal mass in adult polycystic CKD	Plasma creatinine and electrolytes, eGFR: urine dipstick for blood and protein, urinary albumin: Creatinine ratio, renal ultrasound
Renovascular disease			
Atherosclerotic renovascular disease	1-10%	Older: widespread atherosclerosis (especially PAD); diabetes; smoking; recurrent flash pulmonary oedema; abdominal bruit	Duplex renal artery Doppler or CT angiography or MR angiography
Fibromuscular dysplasia		Younger; more common in women; abdominal bruit	

MC Cause of 2° HTN in

- Children (<12 years) – Renal parenchymal disease >Coarctation of aorta
- Adolescence (12-19 years) – Renal parenchymal disease > Coarctation of aorta
- Young adults (20 – 39 year) – Renal parenchymal disease > RAS
- middle age adults (>40 years) – Conn's syndrome > OSAS > Renal parenchymal disease
- Elderly (>60 years) – Atherosclerotic RAS > Renal parenchymal disease

Case scenario

⇒ A 40-year-old male having no comorbidities, no other disease and no symptoms was incidentally detected with BP 160/100

↓

First step is to confirm HTN by 24-hour ambulatory BP

↓

Look for Target organ Damage (TOD)

- TOD disproportionate to degree and duration of HTN is always Secondary

Investigation

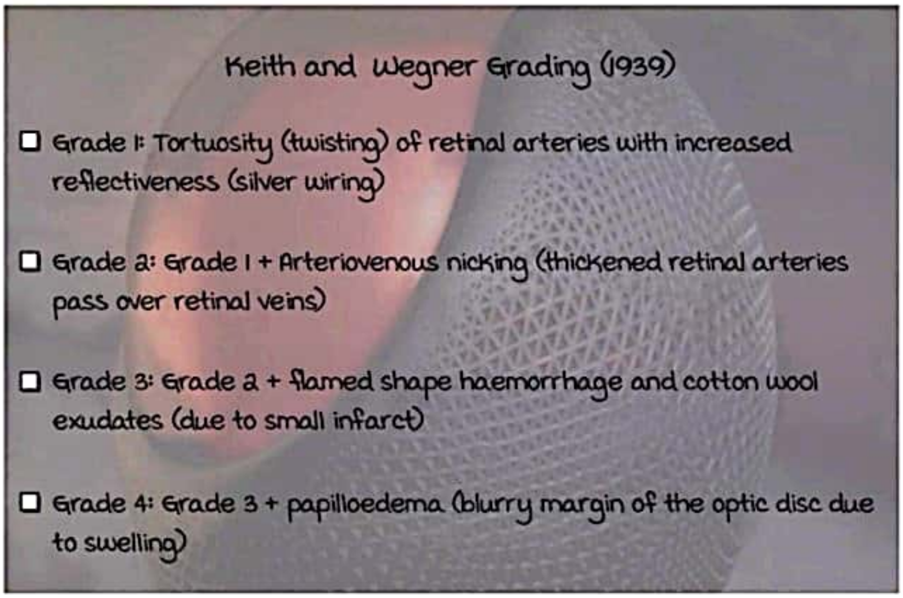
- Renal function test(RFT)
- Ultrasound (USG) abdomen
- Thyroid function test(TFT)
- Parathyroid hormone(PTH) level
- Na^+, K^+
- 24-hour urine fractionated metanephrine

To assess TOD

- Echocardiogram: Look for Left ventricular hypertrophy (LVH)
- Ophthalmic evaluation: Hypertensive retinopathy

Classification of hypertensive retinopathy

00:24:05 51



Keith and Wegner Grading (1939)

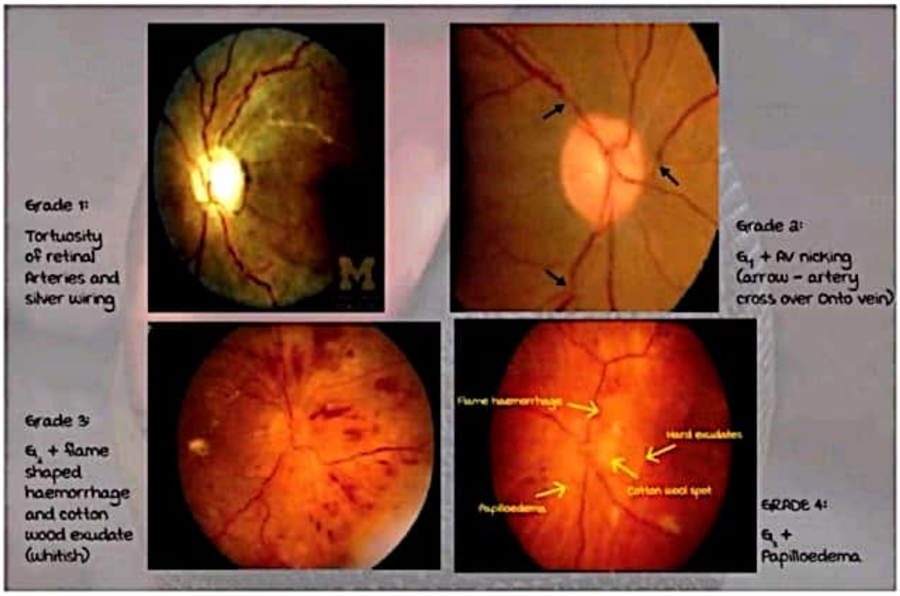
☐ Grade 1: Tortuosity (twisting) of retinal arteries with increased reflectiveness (silver wiring)

☐ Grade 2: Grade 1 + Arteriovenous nicking (thickened retinal arteries pass over retinal veins)

☐ Grade 3: Grade 2 + flamed shape haemorrhage and cotton wool exudates (due to small infarct)

☐ Grade 4: Grade 3 + papilloedema (blurry margin of the optic disc due to swelling)

Warning : Not all points are covered in the notes, especially conceptual explanations. Please use the notes in conjunction with Marrow Edition 4 videos.

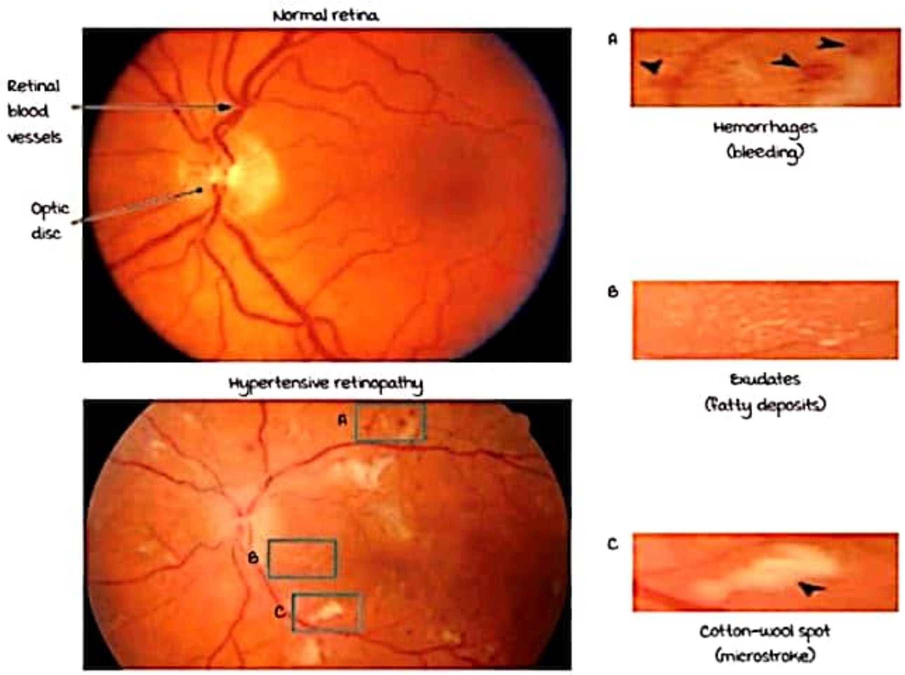


Grade 1:
Tortuosity of retinal Arteries and silver wiring

Grade 2:
G_1 + AV nicking (arrow - artery cross over onto vein)

Grade 3:
G_2 + flame shaped haemorrhage and cotton wood exudate (whitish)

GRADE 4:
G_3 + Papilloedema


Normal retina
Retinal blood vessels
Optic disc
Hypertensive retinopathy
A
B
C
A
Hemorrhages (bleeding)
B
Exudates (Fatty deposits)
C
Cotton-wool spot (microstroke)

Definitions

00:26:26

I. Hypertensive urgency:
- BP >180/120 without any evidence of TOD
- Requires only oral therapy

II. Hypertensive Emergency
- Acute medical emergency
- Diastolic BP >120 mmHg (systolic BP >180 mmmHg) with TOD
- Requires i.v. drugs

III. Accelerated hypertension:
- Hypertensive emergency with new onset changes in fundus

- Flame shaped hemorrhage
- Cotton wool spots – Are soft exudate. It is a pseudo exudate. It is due to stasis of axoplasmic flow in the outer nerve fibre layer of retina
- Hard Exudate:
  - True exudate
  - It is due to exudation of fluid from capillary.

IV. Malignant Hypertension
- Accelerated hypertension + papilledema

Active space

Resistant hypertension

- Hypertension despite being on optimal dose of 3 anti-hypertensives of which one is diuretic
- Resistant hypertension is related to 2° hypertension

Resistant hypertension

Recommendations	Class*
It is recommended that hypertension be defined as resistant to treatment (i.e. resistant hypertension) when: • Optimal doses (or best-tolerated doses) of an appropriate therapeutic strategy which should include a diuretic (typically an ACE inhibitor or an ARB with a CCB and a thiazide/thiazide-type diuretic), fails to lower clinic SBP and DBP values to <140 mmHg and/or <90 mmHg respectively: and • The inadequate control of BP has been confirmed by ABPM or HBPM; and • After exclusion of various causes of pseudo-resistant hypertension (especially poor medication adherence) and secondary hypertension	I
Recommended treatment of resistant hypertension is: • Reinforcement of lifestyle measures, especially sodium restriction • Addition of low-dose spironolactone to existing treatment; • Or the addition of further diuretic therapy if intolerant to spironolactone. with either eplerenone, 'amiloride' a higher dose thiazide/thiazide-like diuretic, or a loop diuretic • Or the addition of bisoprolol or doxazosin	I

Recommendations from Association of physicians of India 00:32:22

- HTN can be diagnosed at the first visit only if the patient presents in hypertensive emergency
- On the second visit, a diagnosis of HTN can be made only if BP > 180/110 or BP > 140/90 mmHg with TOD / CKD / DM
- On third visit, if BP >160/100 mmHg it is equal to hypertension

Assessment of Target Organ Damage (TOD) 00:34:53

I. Microalbuminuria

⇒ It is defined as

- 24-hour urine albumin (best)– 30 to 300 mg or
- Early morning spot urine albumin creatinine ratio(ACR) 30 mg/g to 300 mg/g

⇒ Microalbuminuria indicates

- Endothelial dysfunction
- Target organ damage
- ↑ risk of thromboembolic events in future

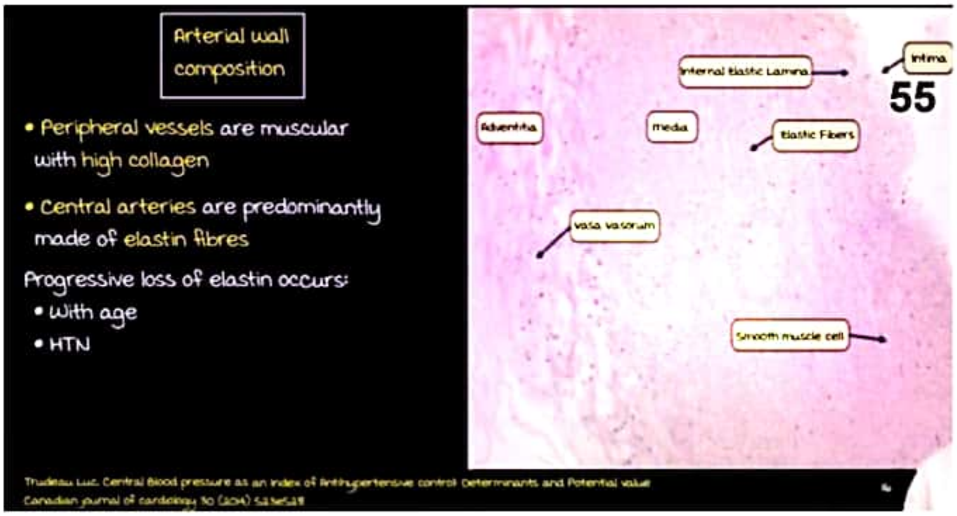
⇒ Patient should be started on ACE inhibitors /ARB's should be started

II. Arterial Aging

- Every heart beat generates a pulse wave, which disperses in the human body. Young and healthy vessels are absorbing the energy of the wave – cushioning effect
- Vessels are ageing. over time they are getting stiff – Vascular walls are not cushioning anymore. The travel speed of the pulse wave is increasing (Pulse Wave Velocity – PWV)
- Early detection of vascular aging is important to prevent CVD in hypertension
- Vascular ageing is not proportional to chronological age.

Arterial stiffness (best marker of TOD)

- Reflects the true arterial wall damage
- Has an independent predictive value for cardio vascular events, independent of the traditional risk factors
- A marker of earlier TOD compared to LVH and albuminuria



Arterial wall composition

- Peripheral vessels are muscular with high collagen
- Central arteries are predominantly made of elastin fibres

Progressive loss of elastin occurs:

- With age
- HTN

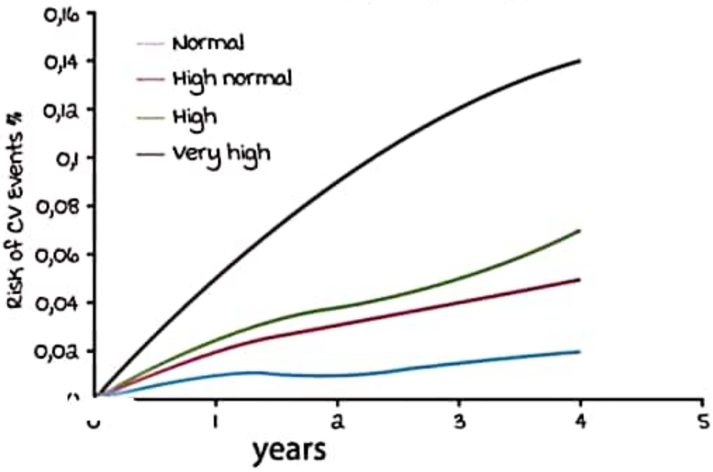
Intima
Internal Elastic Lamina
55
Adventitia
media
Elastic Fibers
vasa vasorum
Smooth muscle cell

Trudeau Luc. Central Blood pressure as an index of Antihypertensive control: Determinants and Potential value Canadian journal of cardiology 30 (2014) S23-S28

III. Central aortic BP

- Better correlated with
  - Carotid internal diameter and intima – media thickness
  - Vascular hypertrophy
  - Extent of atherosclerosis
- Augmentation pressure associated with ↑LVH. Independent of age and MAP
- High central aortic BP and high pulse wave velocity indicates TOD
- Central aorotic BP is the best marker for TOD
- Evaluation of the patient – fundus >LVH > microalbuminuria > central aortic BP

Aortic pulse wave velocity and probability of a CV event



Assessment of arterial stiffness

00:44:36

- Pulse wave Velocity – Gold standard
- Central aortic pressure
- Augmentation index

⇒ Increased arterial stiffness: ↓ Coronary venous perfusion
↑ Afterload
↑ LVH
↑ O_2 demand
Promotes endothelial dysfunction

Speed of the wave is related to the stiffness of the artery it is travelling in

↓

The stiffer the artery;
the higher the wave speed

↓

Wave speed is proportional to the square root of arterial stiffness

Beta-blockers are not effectively protective against cardiovascular events as it increases central systolic pressure

Table: Comparative effect of anti-hypertensive drugs and nitrates on central systolic pressure

Class	Central systolic pressure
ACE inhibitors	↓
Angiotensin receptor blockers(ARB)	↓↔
Beta-blockers	↑↑
Calcium channel blockers	↓↔
Diuretics	↔
Nitrates	↓↓

- mnemonic- A,B,C,D

Management of primary hypertension

00:49:45 57

I. Life style modification

1. weight loss

2. Regular aerobic activity for atleast 30 min/day

3. DASH Plan

- Dietary approach to stop Hypertension
  - Low in red meat and saturated fat
  - Fruits, vegetables, nuts, low fat dairy products
  - Salt < 5g /day
  - Limit alcohol intake

II Drug Therapy

A → ACE inhibitor / ARB

B → Beta blocker

C → Calcium channel blockers(CCB)

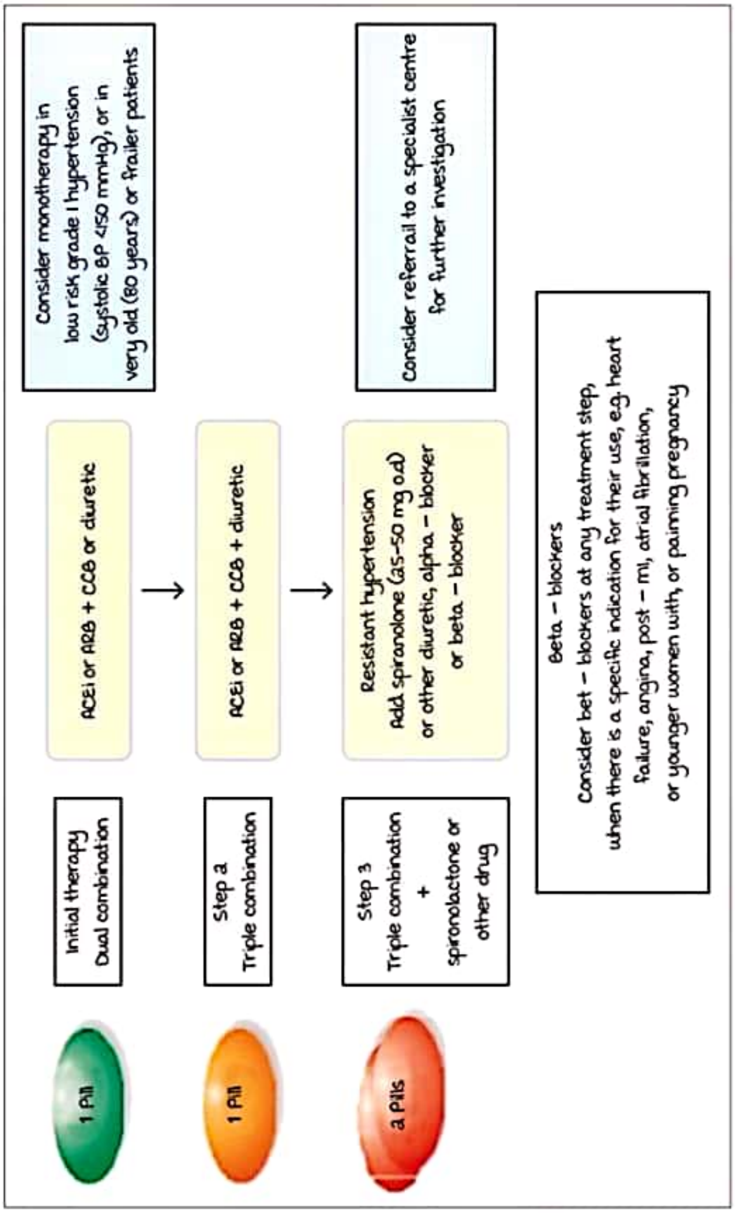
D → Diuretics

⇒ Beta blockers are not first line drugs for uncomplicated HTN
So for uncomplicated HTN ⇒ A, C, D are used

⇒ As per European society of Hypertension (ESH)

- Combination therapy is better for uncomplicated HTN (single drug therapy- no role)

Active space


1 Pill
Initial therapy
Dual combination
ACEi or ARB + CCB or diuretic
Consider monotherapy in low risk grade I hypertension (systolic BP <150 mmHg), or in very old (80 years) or frailer patients
1 Pill
Step 2
Triple combination
ACEi or ARB + CCB + diuretic
2 Pills
Step 3
Triple combination
+
spironolactone or other drug
Resistant hypertension
Add spironolactone (25-50 mg o.d) or other diuretic, alpha – blocker or beta – blocker
Consider referrail to a specialist centre for further investigation
Beta – blockers
Consider bet – blockers at any treatment step, when there is a specific indication for their use, e.g. heart failure, angina, post – mi, atrial fibrillation, or younger women with, or palming pregnancy

⇒ In Hypertension + Coronary artery disease(CAD)

- First line: A + B (Preferred) or A + C
- If not responding then A + B + C → Diuretics → DOC-Spironolactone/Eplerenone⇒ In Hypertension + Chronic Kidney disease(CKD)
- A + C or A + D → A + C + D
- If resistance → Spironolactone, α – blocker

⇒ In Hypertension + Systolic heard failure

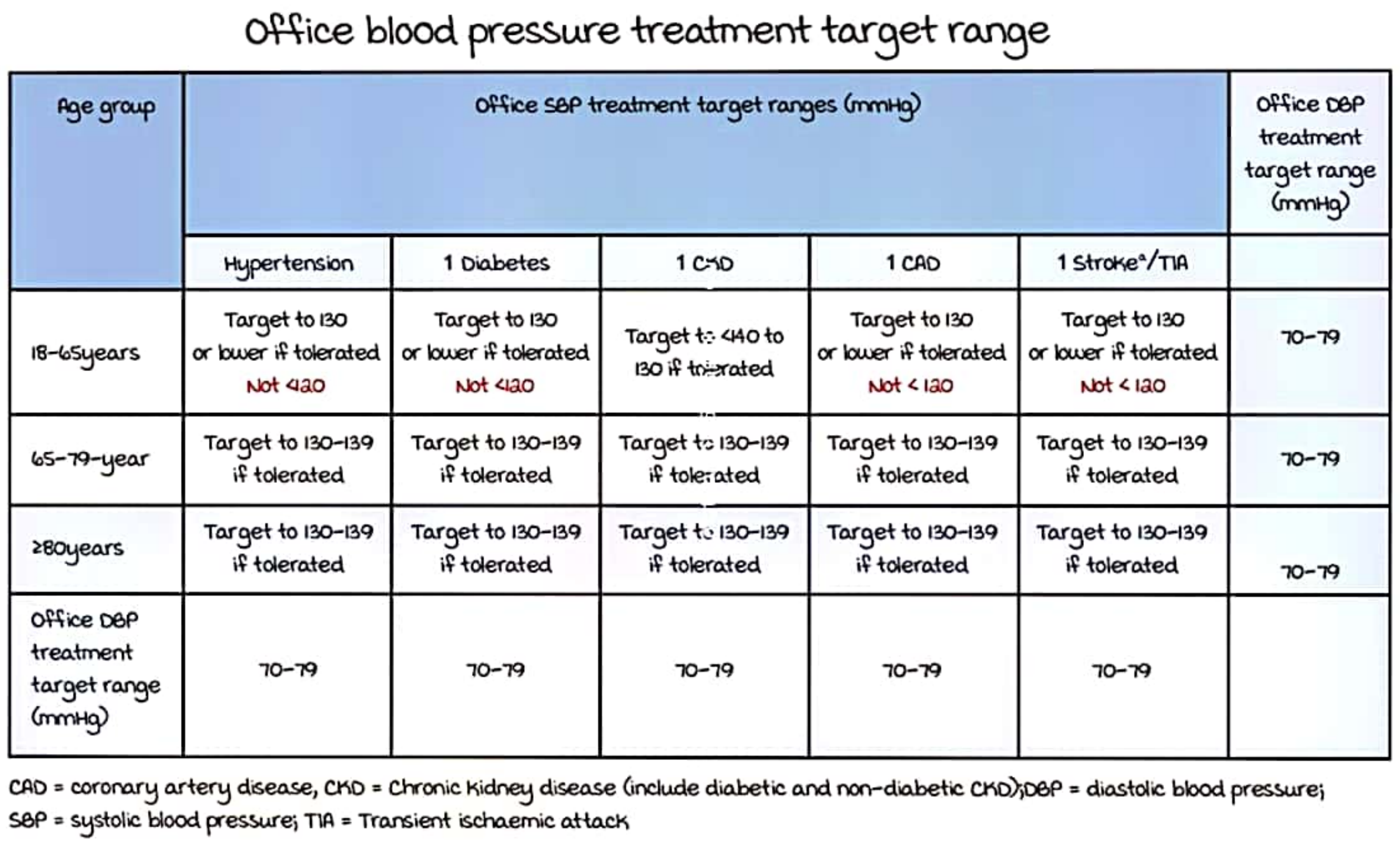
- A + D + B

Note:

- Control of SBP is more important than DBP
- Low diastolic BP is dangerous
  (∵ Coronary perfusion = DBP – Coronary venous pressure)

Office BP treatment target range

01:00:37 59



Office blood pressure treatment target range

Age group	Office SBP treatment target ranges (mmHg)					Office DBP treatment target range (mmHg)
	Hypertension	1 Diabetes	1 CKD	1 CAD	1 Stroke[a]/TIA	
18–65years	Target to 130 or lower if tolerated Not <120	Target to 130 or lower if tolerated Not <120	Target to <140 to 130 if tolerated	Target to 130 or lower if tolerated Not < 120	Target to 130 or lower if tolerated Not < 120	70–79
65–79-year	Target to 130–139 if tolerated	Target to 130–139 if tolerated	Target to 130–139 if tolerated	Target to 130–139 if tolerated	Target to 130–139 if tolerated	70–79
≥80years	Target to 130–139 if tolerated	Target to 130–139 if tolerated	Target to 130–139 if tolerated	Target to 130–139 if tolerated	Target to 130–139 if tolerated	70–79
Office DBP treatment target range (mmHg)	70–79	70–79	70–79	70–79	70–79	

CAD = coronary artery disease, CKD = Chronic kidney disease (include diabetic and non-diabetic CKD);DBP = diastolic blood pressure; SBP = systolic blood pressure; TIA = Transient ischaemic attack

Hypertensive crisis

01:05:41

Four forms

1. Hypertensive urgency
2. Hypertensive emergency
3. Accelerated Hypertension
4. Malignant Hypertension

⇒ Key points to be considered in hypertensive crisis

- Rate of rise of BP
- Rapidity in rise of BP
- Length of time when BP is high
- Degree of TOD

Note:

⇒ Hypertensive emergencies are due to 2° hypertension unless proved otherwise

Examples

1. Acute pulmonary edema:
   - MC hypertensive emergency
   - If there is no cardiac cause, it can be frequently associated with RAS(flash pulmonary edema)
2. Hypertensive encephalopathy:
   - Posterior reversible encephalopathy syndrome (PRES)
   - HTN is due to ↑ Cerebral edema
3. Malignant Hypertension
   - Causing thrombotic microangiopathy with acute kidney injury(AKI)
4. Pre – eclampsia /HELLP Syndrome
5. Acute aortic dissection

Drugs for Hypertensive Emergency

I. Metoprolol – Selective β_1 blocker
   Esmolol – Ultrashort acting β – blocker
   Labetalol – $\alpha + \beta$ blocker

II. Calcium channel blocker: Nicardipine
    Clevidipine (Ultra short acting)

III. Fenoldopam (D_1 agonist)

IV. Sodium nitroprusside

V. Nitroglycerin

VI. Urapidil, Phentolamine, Clonidine, Enalaprilat

Management of Hypertensive Emergency

1. Acute pulmonary Oedema

- Nitroglycerin: infusion- 5 µg/min → 25 µg /min
  aim-to immediately reduce systolic BP < 140 mmHg
  or
- Sodium nitroprusside: 0.25-0.5 mg/kg/min infusion

2. Hypertensive encephalopathy / malignant hypertension / HELLP

  - Labetalol : 20 mg i.v bolus over 2 min (can repeat upto 2-3 times then 2mg/min infusion) or
  - Nicardipine : Start with 5 mg/hr infusion

- Reduce MAP by 20-25% in hypertensive encephalopathy (MAP=DBP + 1/3rd of pulse pressure)
- Reduce BP over several hours in malignant hypertension
- Immediately reduce systolic BP to <150 -160 mmHg in HELLP

3. Acute aortic dissection

- Immediately reduce SBP < 120 mmHg
- Esmolol + Nitroprusside or Nitroglycerin + Nicardipine

Nitroglycerine	1-5 min	3-5 min	5-200 mg/min, 5mg/min increase every 5 min		Headache, reflex tachycardia
Nitroprusside	Immediate	1-2 min	0.3-10 mg/kg/min, increase by 0.5 mg/kg/min every 5 min until goal BP	Liver/kidney failure (relative)	Cyanide intoxication
Enalaprilat	5-15 min	4-6 h	0.62-1.25 mg I.V.	History of angioedema	
Urapidil	3-5 min	4-6 h	12.5-25 mg as bolus injection, 5-40 mg/h as continuous infusion		
Clonidine	30 min	4-6 h	150-300 mg I.V. over 5-10 min		Sedation, rebound hypertension
Phentolamine	1-2 min	10-30 min	0.5-1 mg/kg bolus injections or 50-300 mg/kg/min as continuous infusion		Tachyarrhythmias, chest pain

Drugs for hypertension

01:19:11

1. Diuretics

- Thiazide diuretics (vasodilatory action ⇒ ↓peripheral resistance)
- Hydrochlorothiazide is now replaced by chlorthalidone (long acting)
- Only thiazide diuretic safe to use in renal failure is metolazone

Adverse effects: Hyponatremia
Hyperuricemia
Hyperglycemia
Hypercalcemia
Sexual dysfunction in young
Not safe in renal failure

Indapamide (2.5mg): It ↓ central systolic BP
very less metabolic side effects
low risk of hyponatremia

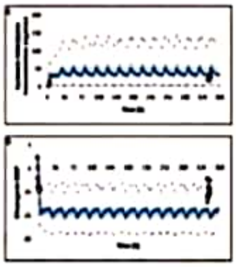
II. Calcium channel Blocker

1. Phenylalkylamine: Verapamil, diltiazem ⇒ Not used for HTN
2. Dihydropyridine
   - L -type of CCB

Active space

  - Peripherally acting vasodilators
  - Produce reflex tachycardia

- Long acting: Amlodipine (causes pedal edema)
- Short acting: Nifedipine (very potent)



Coronary steal syndrome by nifedipine

- Rapid onset of action <20 min
- Produces brisk precipitous fall in BP
- Drug induced hypotension - can activate severe reflex tachycardia, which can worsen the myocardial ischaemia by increasing the myocardial ocygen demand and decrease myocardial oxygen demand (by decreasing the diastolic oxygen filling time)

⇒ Cilnidipine:

  - 4th generation L + N type calcium channel blocker
  - Reduces proteinuria
  - Less reflex tachycardia

⇒ Benidipine

  - L + N + + type CCB
  - ↓ proteinuria
  - Less reflex tachycardia

Drugs for hypertension III / ACE Inhibitor / ARB & others

01:28:31

III. ACE Inhibitor / ARB:

- ACE Inhibitor:
  - ↓ central systolic BP
  - block AT-2
  - In case of Cough & angioedema (due to bradykinin → Switch to ARB)
  - Drugs: Ramipril 2.5 mg → 5mg → 10mg
    Perindopril 4 mg
- ARB: No action on central systolic BP
  - it does not block AT-2

- Drugs: Losartan: uricosuric effect
  Telmisartan: Long t ½
  Azilsartan: High affinity to receptor

⇒ Absolute contraindication for ACEI/ARB

1. Pregnancy
2. Bilateral RAS
3. History of herediatary angioneurotic edema

⇒ ACE Inhibitor should be stopped if serum creatinine raises by ≥30% (within 1 week of start of the drug) or if serum $K^+ > 6$ m Eq/litre within one week of starting drug

Fimasartan (30 mg, 60 mg)

- Losartan derivative where imidazole ring has been replaced
- 600 times more affinity to $AT-2_1$ receptor
- No partial agonistic action on AT_2
- Longer duration of action

For uncomplicated Hypertension

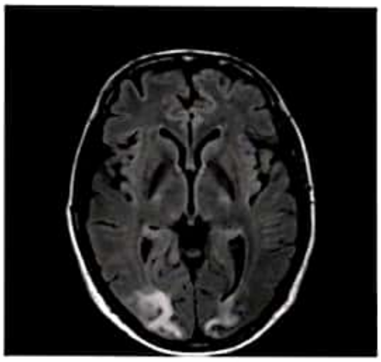
Fimasartan (30 mg) or Azilsartan (40 mg)
+
Benidipine 4 mg
Or
Indopamide 2.5 mg

Nebivolol

- Highly selective β_1 blocker
- NO donor from endothelium
- Anti – oxidant
- Effectively lowers central aortic pressure
- Single dose
- No major adverse effects

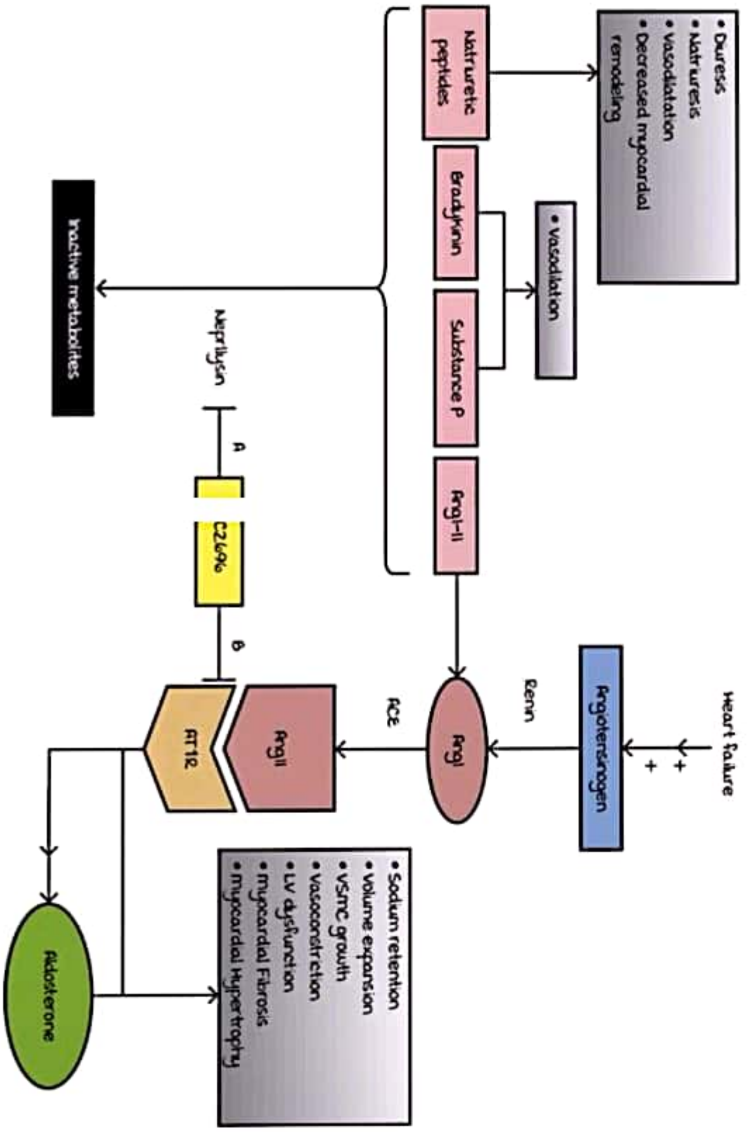
Posterior reversible encephalopathy syndrome (PRES) 01:34:31

- Hyperintensity seen on T_a – FLAIR MRI
- Characterized by white matter edema



Angiotensin receptor neprilysin inhibitor (ARNI) 01:35:15

- Angiotensin Receptor Neprilysin Inhibitor
- Valsartan + sacubitril


Natruretic peptides
Bradykinin
Substance P
AngI-II
• Duresis
• Natruresis
• Vasodilatation
• Decreased myocardial remodeling
• Vasodilation
Inactive metabolites
Neprilysin
A
CZ696
B
Heart failure
+
+
Angiotensinogen
Renin
AngI
ACE
AngII
AT1R
• Sodium retention
• Volume expansion
• VSMC growth
• Vasoconstriction
• LV dysfunction
• myocardial Fibrosis
• myocardial Hypertrophy
Aldosterone

LCZ696 – Sacubitril / Valsartan – Entresto

Active space

MITRAL VALVE APPARATUS AND MITRAL STENOSIS

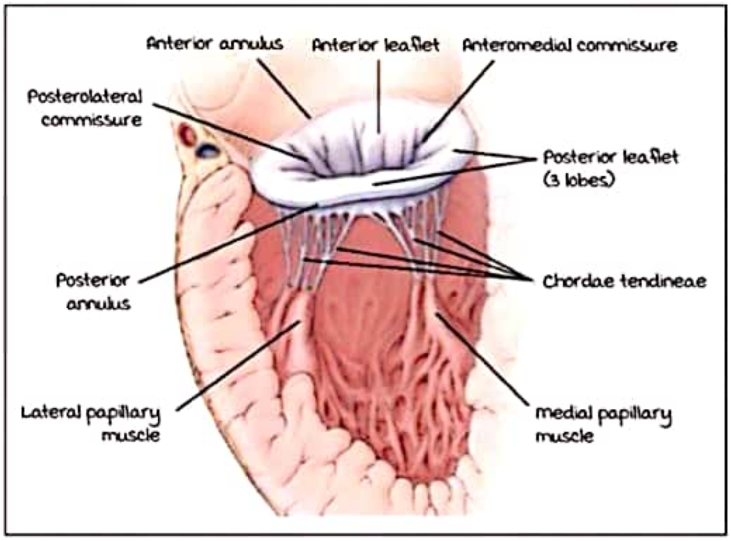
Mitral valve apparatus 00:00:08

The mitral valve apparatus consists of

- Annulus
- Leaflets (anterior and posterior)
- Commissure (anteromedial and posterolateral)
- Chordae tendineae (1°,2°,3°)
- Papillary muscle (Posteromedial and anterolateral)

I. Annulus

- Asymmetrical, elliptical
- Anterior ⅓ – Fibrous portion (continuous with aortic annulus)
- Posterior ⅔ – muscular


Anterior annulus
Anterior leaflet
Anteromedial commissure
Posterolateral commissure
Posterior leaflet (3 lobes)
Posterior annulus
Chordae tendineae
Lateral papillary muscle
medial papillary muscle

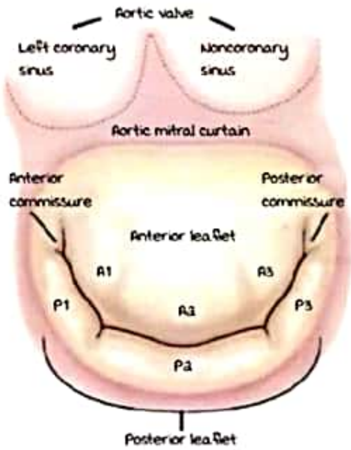
The mitral valve apparatus consisits of the mitral annulus, anterior and posterior leaflets, chordae tendineae, and the papillary muscles

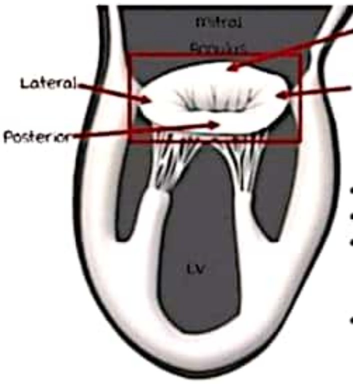
II. Leaflets:

- Anterior leaflet – Thicker
  larger surface area
  A_1, A_2, A_3
- Posterior leaflet – Thinner
  smaller
  more prone for MVP mitral valve prolapse

Active space

⇒ Leaflets are separated by Commissures

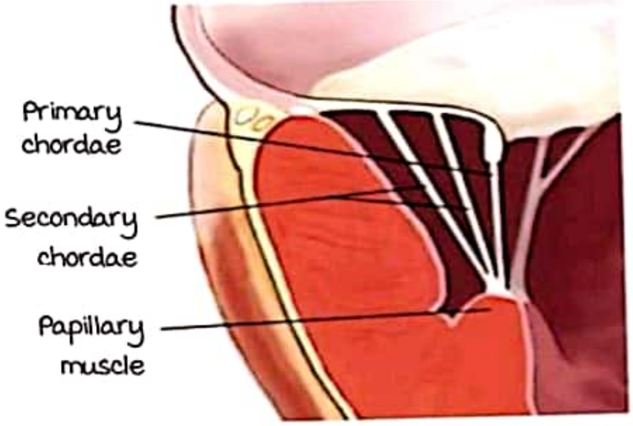

Aortic valve
Left coronary sinus
Noncoronary sinus
Aortic mitral curtain
Anterior commissure
Posterior commissure
Anterior leaflet
A1
A2
A3
P1
P2
P3
Posterior leaflet


Mitral Annulus
Anterior
Lateral
medial
Posterior
LV

- Saddle Elliptical shape
- Anchor for leaflets
- Superiorly orientated: Anterior & Posterior (towards LA)
- Inferiorly orientated: medial & Lateral (towards LV)

III. Chordae

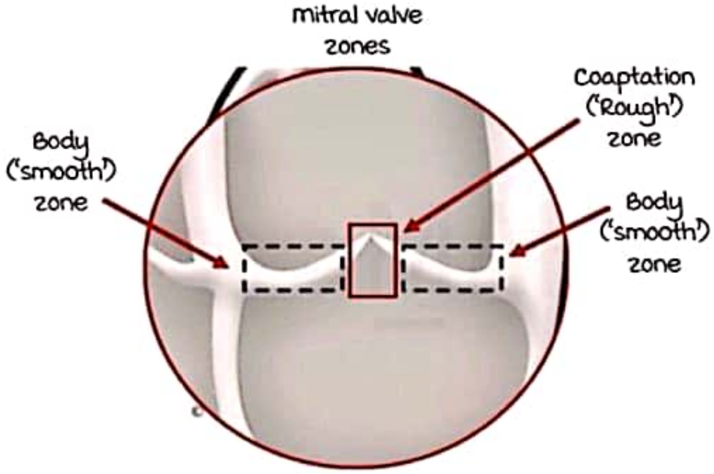
- The normal valve has an average of 25 primary chordae
- Primary chordae tendineae attach to leaflet tips
- Secondary chordae tendineae attach to leaflet body
- Tertiary chordae attach to leaflet base


Primary chordae
Secondary chordae
Papillary muscle

IV. Papillary muscles

- The chordae attach to the two papillary muscles (anterolateral and posteromedial) affixed to the LV wall
- Posteromedial papillary muscle → single blood supply → commonly involved in IWMI > AWMI
- Posteromedial papillary muscle rupture can lead to acute MR

mitral valve closure


mitral valve zones

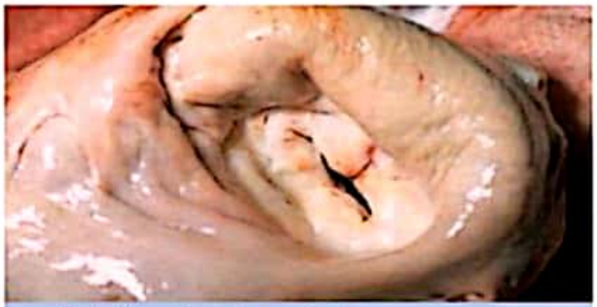
1. Anterior leaflet forming a veil which is parallel to systolic flow in the LV tract
2. Coaptation of two leaflets
3. Posterior annulus contraction → approximating 2 leaflets → enhances coaptation

⇒ Loss of Coaptation can result in MR (soft S_1)

Mitral stenosis

00:11:49

mitral stenosis


mitral stenosis with marked thickeninig of the leaflets and left atrial hypertrophy

Causes

1. Acute Rheumatic fever – 40% patients with rheumatic valvulitis develops MS predominant heart disease (takes approximately 2 years)
2. Congenital MS – cor triatriatum
   Parachute mitral valve
3. Left atrial myxoma

4. Autoimmune: SLE, RA

   Note: The MC valvular heart disease in SLE and RA is MR

5. Large Infective endocarditis (large vegetations)

6. Calcified mitral valve

Pathogenesis

- Chronic inflammation with diffuse thickening of valve leaflets results in fibrous tissue formation
- commissures and chordae → fuse & shorten → fish mouth appearance of valve
- Calcification of stenotic valve will further immobilize valve leaflet and worsen stenosis. This leads to thrombosis and thromboembolism

Note: MC site for thromboembolism is left atrial appendage

Severity of MS

00:18:27

Severity of MS

Normal mitral valve surface area - 4-6 cm^2

mild MS	- > 1.5 cm^2
moderate MS	- 1-1.5 cm^2
Severe MS	- < 1 cm^2

1. mild MS

- slight increase in left atrial pressure (to maintain cardiac out put). patient - asymptomatic
- when heart rate increases → diastole shortens → increase in left atrial pressure(LAP) → increase pulmonary venous pressure --> dyspnoea on exertion(first symptom in MS)
- Left atrial pressure ⇒ Normal to slightly ↑

  Pulmonary arterial pressure & cardiac output ⇒ Normal

moderate MS

1. Left atrial pressure (LAP) increased at rest
2. Pulmonary venous pressure (PVP) or PCWP is increased
3. Due to back pressure, Pulmonary artery pressure ↑ (30-50 mmHg)

4. Thus pulmonary hypertension develops which leads to RVH

⇒ Due to ↑ LAP
↓
Electrical & mechanical activity of LA is altered

- Atrial Fibrillation ⇒ Palpitation, thromboembolism
- Dyspnea with minimal activity --> lead to orthopnea and PND

⇒ Due to pulmonary Hypertension

- Loud, palpable P2
- Due to RVH ⇒ JVP elevated (Prominent 'a' wave)
  Functional TR (Prominent 'v' wave)
- Parasternal heave
- Epigastric, suprasternal, 2nd left ICS pulsation

Severe MS

- LAP ↑↑
- Pulmonary artery pressure ↑↑
- RVH ↑↑
- RV failure (ascites, edema, hepatomegaly)
- CO begins to decrease

Note:

In very severe MS – CO decreases further, LV failure

Clinical findings in MS 00:29:48

- Pulse: Normal (except in atrial fibrillation – irregular)
- BP: Normal (low BP in very severe MS due to ↓ CO)
- JVP: Elevated in moderate MS
  'a'– wave: Pulmonary hypertension
  'v'– wave: Tricuspid regurgitation
- Edema: Seen in severe MS (due to RV failure)
- Inspection: Elevated JVP
- Palpation: Palpable P_2, left parasternal heave, pulsations, tapping apex, no cardiomegaly (slightly laterally displaced)

- S_1 : Loud S_1
- S_2 : Loud palpable P_2 (wide split S_2 in RV failure)
- S_3 : Not heard
- S_4 : Not heard
- Added sound: opening Snap

First rank symptoms

- Dyspnea
- Palpitations (due to atrial fibrillation)

Note: Angina and syncope are unlikely to be seen in MS

Second rank symptoms

- Edema, ascites (due to RV failure)
- Hemoptysis (due to ↑ LA pressure: rupture of bronchial veins)

Persistent cough (due to pulmonary venous congestion)

- Hoarseness of voice (Ortner syndrome: due to dilated LA compressing recurrent laryngeal nerve)
- Orthopnea, PND (due to ↑ LA pressure)
- Purplish discolouration of face- mitral facies-due to ↓ co.

Normal valve area 4–6 cm^2

AHA Guidelines for severity of mitral stenosis

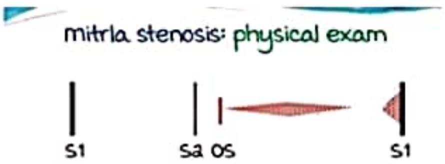
	Valve Area (cm^2)	systolic pulmonary artery pressure (mmHg)	mean pressure Gradient (mmHg)
mild	> 1.5	< 30	< 5
moderate	1.0–1.5	30–50	5–10
Severe	< 1	> 50	> 10

Note:

- 2 decade long latent period from the onset of rheumatic fever to the development of MS
- By 4th decade patient is symptomatic
- Symptomatic patient --> no intervention --> death in 2-5 years

Murmur in MS

- Low pitch
- Rough and rumbling
- Heard at apex
- Associated thrill
- mid-diastolic murmur (MDM)
- Best heard with bell of stethoscope
- Heard in left lateral position
- Best heard in expiration
- Associated with loud S1, with opening snap
- Not radiating to axilla
- Pre-systolic accentutation



mitrla stenosis: physical exam

- First heart sound (S_1) is accentuated & snapping
- Opening snap (OS) after aortic valve closure
- Low pitch diastolic rumble at the apex
- Pre-systolic accentuation (esp. if in sinus rhythm)

Differential diagnosis for MDM

1. Tricuspid stenosis: TS murmur increases with inspiration
   Best heard at left lower sternal border

2. Carey coombs murmur:
   - Seen in acute rheumatic fever with valvulitis
   - Soft MDM
   - Absence of loud S_1
   - Soft S_1
   - Cardiomegaly
   - Predomi[illegible]
   - No opening snap or thrill

3. Austin flint murmur:
   - Functional low-pitched MDM heard in aortic regurgitation when regurgitant jet hits the anterior mitral leaflet
   - Best heard at apex
   - No loud S_1, opening snap or thrill
   - Peripheral signs of AR +

Associated murmurs in MS

- Pansystolic murmur of TR – Best heard at left lower sternal border. Carvallo's sign (↑ in intensity with inspiration)

- High pitched diastolic decrescendo blowing murmur heard along the left sternal border in case of associated PR. (called Graham steel murmur)

Severity of ms

- Closer the S_2 – OS gap more severe the ms
- Duration of murmur α severity
- As the valve cusps become immobile
    Loud S_1 softens
    - OS disappears
    - When pulmonary hypertension occurs: P_2 intensity ↑, mDm become quieter

Investigations

00:46:15

Transthoracic Echocardiogram

- TTE assesses
    - Orifice area: < 1cm^2 with – severe
    - Pulmonary artery pressure: >50 mmHg with – severe
    - Transvalvular gradient: >10 mmHg with – severe
    - Associated mR
    - Calcification
    - Thrombus

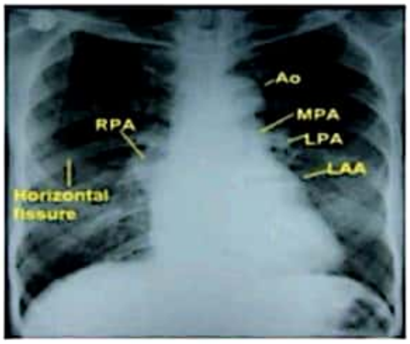
⇒ TEE with – indicated for LA appendage thrombus

⇒ Tumor resembling mS with – LA myxoma

Chest X- Ray

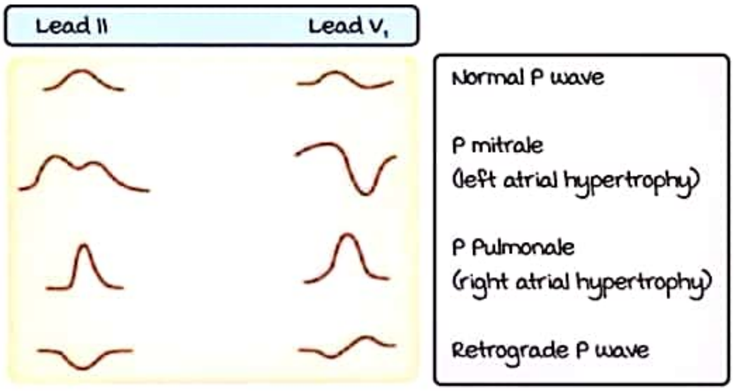
1. Straightening of left heart border
2. Enlarged LA (double shadow)
3. Backward displacement of esophagus by LA
4. Splaying of carina left main bronchus lifted by LA)

CXR



5. Prominent upper zone pulmonary veins
6. Kerley B lines (due to interstitial fluid)

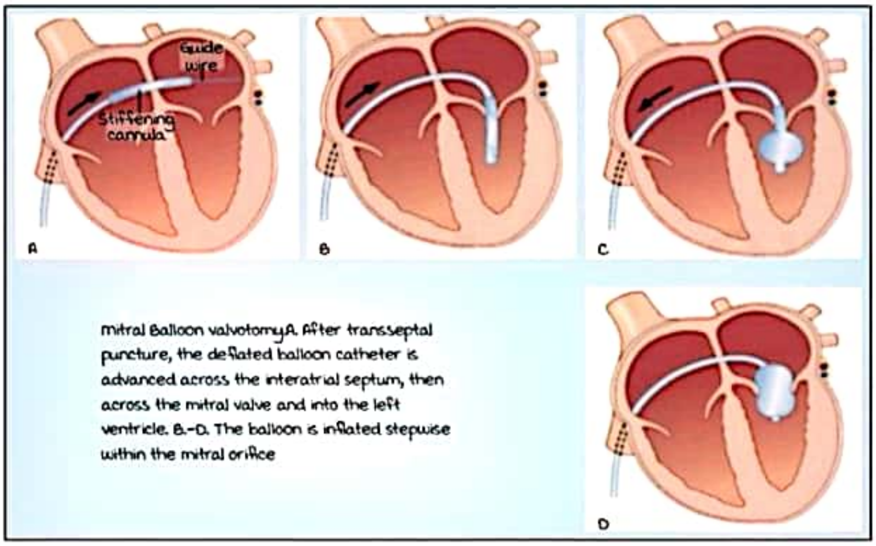
ECG


Lead II
Lead V1
Normal P wave
P mitrale (left atrial hypertrophy)
P Pulmonale (right atrial hypertrophy)
Retrograde P wave

Management of MS

00:51:04

- Warfarin at INR (2-3) to be administered to patients with AF (Paroxysmal, persistent or permanent)
- No role for new oral anticoagulants
- PMBV (Percutaneous mitral Balloon valvotomy)
  - Severe MS – Symptomatic
  - moderate MS – Symptomatic


Guide wire
Stiffening cannula
A
B
C
D

mitral Balloon valvotomyA. After transseptal puncture, the deflated balloon catheter is advanced across the interatrial septum, then across the mitral valve and into the left ventricle. B.-D. The balloon is inflated stepwise within the mitral orifice

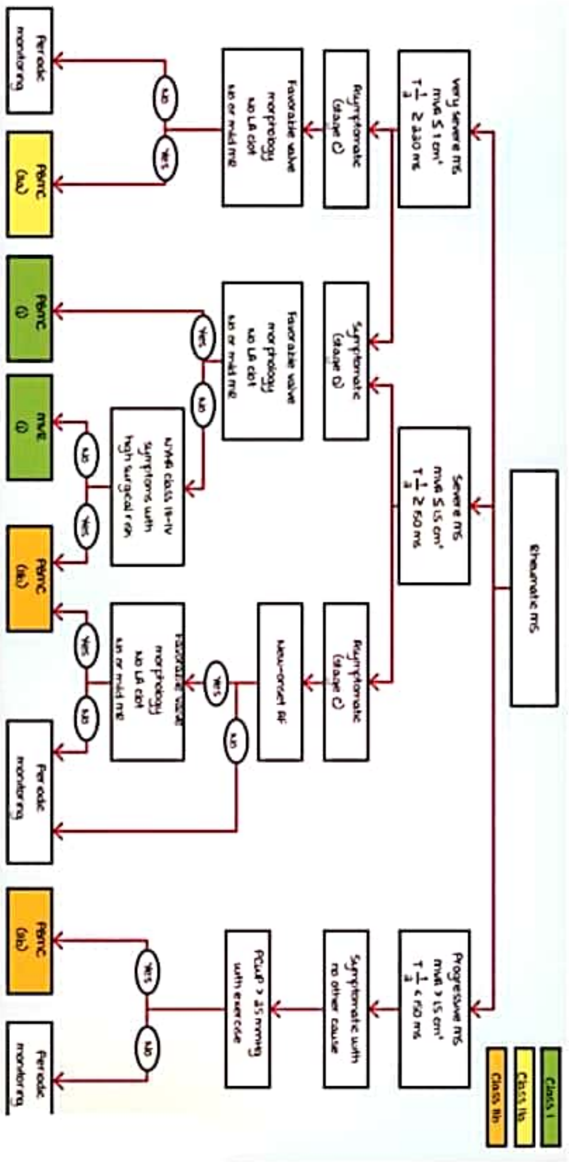
- mitral valve Replacement (MVR)

  necessary if
  - MR is present
  - Badly diseased or badly calcified stenotic valve
  - moderate or severe MS and thrombus in LA despite anticoagulation

Note:

In asymptomatic severe MS: Periodic monitoring done. If PCWP increase to >25 mmHg with exercise → then PMBV is indicated

Recommendations	COR	LOE
PMBC is recommended for symptomatic Patients with severe MS (MVA≤1.5 cm_a stage D) and favorable valve morphology in the absence of Contraindications	1	A
mitral valve surgery is indicated in severely Symptomatic patients (NYHA Class III/IV) with severe MS (mvA ≤1.5 cm_a stage D) who are not high risk for surgery and who are not candidates for or failed previous PMBC	1	B
Concomitant mitral valve surgery is indicated for Patients with severe MS (mvA ≤1.5 cm_a, stage C or D) undergoing other cardiac surgery,	1	C


Rheumatic MS
Very severe MS
MVA ≤ 1 cm²
T½ ≥ 220 ms
Severe MS
MVA ≤ 1.5 cm²
T½ ≥ 150 ms
Progressive MS
MVA > 1.5 cm²
T½ < 150 ms
Asymptomatic
(Stage C)
Symptomatic
(Stage D)
Asymptomatic
(Stage C)
Symptomatic with
no other cause
Favorable valve
morphology
no LA clot
no or mild MR
Yes
No
Favorable valve
morphology
no LA clot
no or mild MR
Yes
No
NYHA class III–IV
symptoms with
high surgical risk
No
Yes
New-onset AF
Yes
No
Favorable valve
morphology
no LA clot
no or mild MR
Yes
No
PCWP > 25 mmHg
with exercise
Yes
No
Periodic
monitoring
PBMC
(IIa)
PBMC
(I)
MVR
(I)
PBMC
(IIb)
PBMC
(IIb)
Periodic
monitoring
PBMC
(IIb)
Periodic
monitoring
Class I
Class IIa
Class IIb

Active space

MITRAL REGURGITATION

- Primary abnormality of one or more components of valve apparatus (Organic MR)
- secondary to LV dysfunction (Functional MR)

- Acute MR
  1) secondary to papillary muscle Rupture (Inferior wall MI > Anterior wall MI)
     Posteromedial papillary muscle rupture
  2) Trauma
- Chronic MR
  - Primary (Organic MR)
    1) myxomatous mitral valve
    2) Rheumatic
       Primary MR is the most common cause
  - Secondary (Functional) [Innocent Bystanders]
    due to LV systolic dysfunction
    - IHD with LV dysfuction
    - Dilated Cardiomyopathy
    - HOCM

>55 yrs of age → m.c cause mcc is degenerative MR (mild MR)

<55 yrs of age → mcc in developed world – MVP

mcc in developing world – RHD

Across all age groups, most common cause for significant MR is always Rheumatic Heart Disease

→ Incidence of MR is 2%

→ Both males and females are affected equally

→ most frequent valve disease in the USA → MR

Primary MR	Secondary MR
Rigid, thickened & deformed valve leaflet + Shortening & Fusion of chordae → Defective coaptation of leaflets → [redacted]	Ventricular Remodelling + Papillary muscle displacement

Carpentiers classification of MR 00:07:53

Type I	Normal valve movement	Annular dilation (Functional MR)
Type 2	↑valve movement	mitral valve prolapse
Type 3	Restricted valve movement	RHD

Other conditions involving mitral valve 00:09:45

Systemic disease

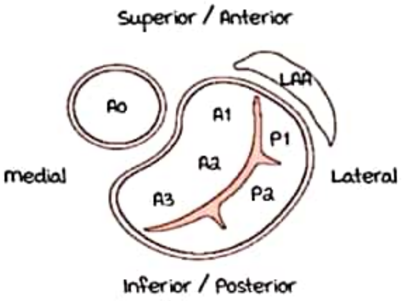
- SLE
- Hypereosinophilic Syndrome
- Amyloidosis
- RA
- Ehler- Danlos syndrome type I and III
- Scleroderma
- Content miss : marfan syndrome - MVP+/-MR

External causes

- Radiation therapy
- Drugs – Fenfluramine
  Phentermine
- methylsergide
- Trauma
- Surgical
- Percutaneous valvuloplasty

Myxomatous MV disease 00:10:57

- Spongy changes affecting both leaflets (Post > Ant)
- Sometimes chordae are affected
- In some patients, associated with mitral valve prolapse [MVP+/-MR] m.c prolapse → Posterior leaflet (middle scallop middle scallop or P2 segment)



Carpentier has provided a surgical classification of mitral valve anatomy that is widely used. In this classification, the mitral valve has six segments, three in the anterior leaflet (A1, A2, and A3) and three in the posterior leaflet (P1, P2, and P3)

Myxomatous changes → MVP+/- MR

Elderly > 60 yrs
- Minimal dilation of annulus
- Thin leaflet
- Thin chordae
- Less calcification
- → mild me mild MR
- (fibroelastic deficiency)

Young < 60 yrs
- Severe annular dilation
- Thickening of leaflet
- Elongated chordae with calcification of leaflet (Barlows Disease)
- → Severe MR

- Young Females
- Defect in Type III collagen
- Marfans and Ehler Danlos syndrome
- Posterior leaflet most commonly prolapses

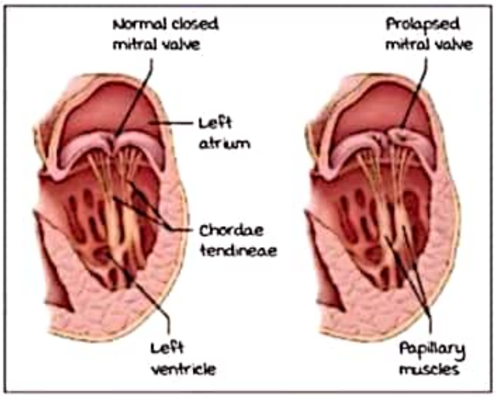
MVP + myxomatous changes

Severe annular Dilation + calcification Barlows disease

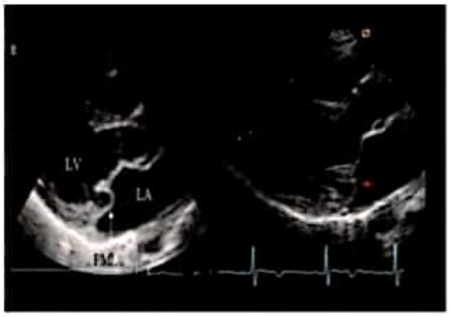
↓ in tensile strength & chordal rupture (due to myxomatous changes in chordae)

Mitral Regurgitation

- Asymptomatic MVP → m.c in Females [illegible]
- Older men have severe MVP + MR
- Most common symptom – Chest pain due tp papillary muscle stretching leading to generation of ventricular ectopics / palpitation
- Non-ejection click due to sudden stretching of chordae tendinae followed by murmur


Normal closed mitral valve
Prolapsed mitral valve
Left atrium
Chordae tendineae
Left ventricle
Papillary muscles

Active space



Heart sounds → only click or ony murmur (click followed by murmur -> most classical murmur)
sometimes both are absent

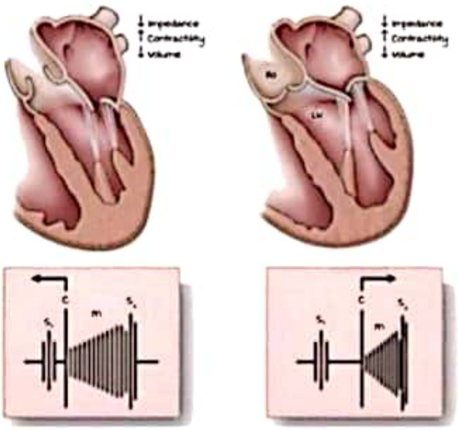
Following Non-ejection click → murmur

Radiates to

Axilla (Anterior leaflet prolapse)

Aortic area (Posterior leaflet prolapse)

- High pitched
- whooping (cooing dove / seagull murmur)
- mid to late systolic apex, crescendo decrescendo



LV volume decreases:
- contractility ↑
- Prolapse ↑
- murmur ↑ intensity ↑
  Duration ↑
- Click and murmur will be closer to S_1

All murmurs
↑ intensity = ↑LV cavity size
Except MVP, HOCM

Active space

MVP v/s HOCM

MVP	HOCM
- Following a Premature ventricular contraction	
MVP murmur remains unchanged/decreases Remains unchanged / decreases	HOCM murmur Increases in intensity and duration
- Straining phase of Valsalva maneuver	
murmur increases in duration	murmur increased in intensity

Pts with MVP without MR require only follow up periodically

MVP with MR require mitral valve repair

Pathophysiology of MR

00:28:45

Blood from LV during systole → Left Atrium LV Systole → Lt Atrium

(LV radius >> thickness)

Priority → maintain Cardiac Output

Compensation → eccentric hypertrophy / dilatation of LV to accept extra amount of blood From LA

No diastolic pathology with LV

↓

(asymptomatic) Excess blood in LV → ↑SV → ↑CO (70%)

no chestpain

no dyspnea

no syncope

Earliest symptom in MR → Palpitation ⊕

Severe MR

C.O (70%) → C.O (60%) CO 60% → LV systolic failure LV systolic Failure

- Fatigue
- Dyspnea
- Hypotension

(Rare – Pulmonary HTN, Acute pulmonary edema)

Clinical findings

- Pulse – Normal, LVF → bounding
  Atrial fibrillation → irregular
- BP – Normal
  Hypotension in severe MR
- JVP – Normal

Inspection – No Findings suggestive of pulmonary HTN

Palpation – apex displaced down and out. (cardiomegaly)
(eccentric hypertrophy)
Forceful / hyperdynamic apex
Palpable thrill → Severe MR

Auscultation

S_1	Reduced zone of coaptation Defective Isovolumetric contraction	soft S_1
S_2	Early A_2, Delayed P_2, wide variable S_2	
S_3	(+)	
S_4	(–)	

MS v/s MR

• Right ventricular hypertrophy	MS
• Pulmonary HTN	MS
• Thromboembolism	MS
• Hemoptysis	MS
• IE	MR

Warning : Not all points are covered in the notes, especially conceptual explanations. Please use the notes in conjunction with Marrow Edition 4 videos.

Acute mitral regurgitation 00:40:49

- Inferior wall MI
- Posteromedial papillary muscle rupture
- Blood regurgitates into a non – compliant LA

↓

↑ LA pressures

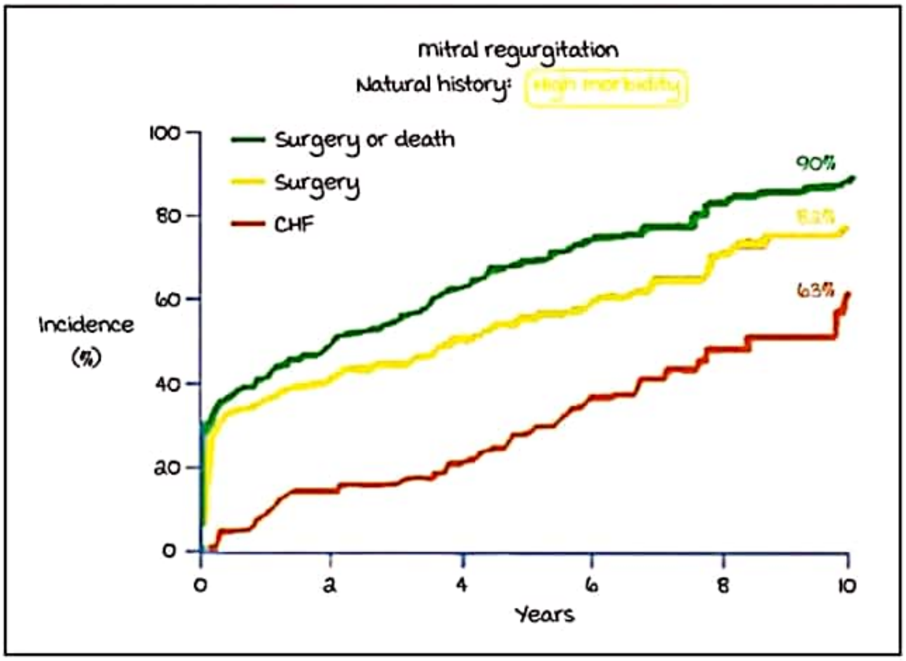
↓

↑ PVP / PCWP → Acute Decompensated pulmonary edema

1) LV cavity Ⓝ
2) murmur – Pansystolic murmur
3) murmur best heard in aortic area
4) JVP elevated

Murmur

- Pansystolic murmur (except Acute MR) Severity ∝ Loudness of murmur
- High pitched
- Soft blowing
- Heart at apex / diaphragm
- Thrill absent
- Conduct to left axilla
- No increase with expiration



Risk of Sudden Cardiac Death

0.8% (asymptomatic with MR)

1.8 – 3% (symptomatic not treated)

Management of MR

00:46:50

mitral valve repaire

Echo criteria : Severe MR	Regurgitant volume	>60ml /beat
	Regurgitant Fraction	>50%
	Effective regurgitant Orifice	$>0.4cm^2$

Symptomatic ⟶ mitral valve repair

EF > 30% Class I recommendation

EF <30% Dmitral Valve repair

Severe MR But asymptomatic

→ Healthy young adult ⟶ mitral valve repair

→ Elderly ⟶ Periodic monitoring, if EF ↓↓ → mitral valve repair

MR not severe ⟶ Periodic monitoring

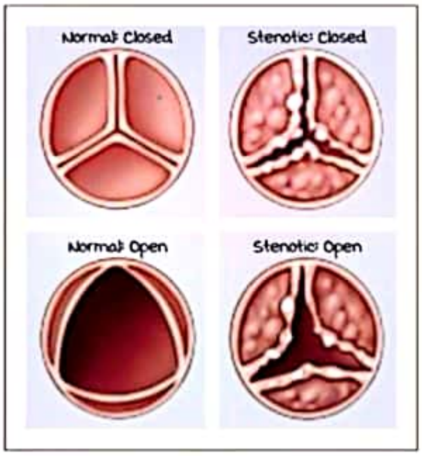
2° MR ⟶ management of LV systolic dysfunction

Afib ⟶ Anti coagulation

AORTIC STENOSIS

Arotic valve 00:00:08

- normal aortic valve surface area: 3-4 cm^2
- 3 valve cusps
- separated by 3 commissures
- cusps are crescent shaped
- narrowing of aortic orifice is called aortic stenosis



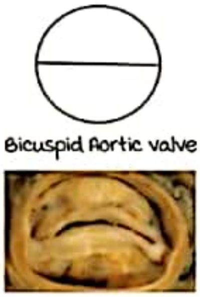
Epidemiology 00:01:29

Age	Aortic sclerosis	Aortic stenosis
65-75 years ⇒	20%	1.3%
75-85 years ⇒	35%	2.4%
>85 years ⇒	48%	4%

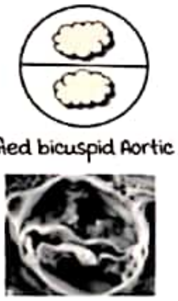
- Aortic sclerosis is very common in the elderly. It is related to atherosclerosis
- Aortic sclerosis means thickening and sclerosed leaflet

Aortic stenosis 00:04:00

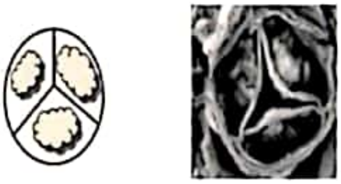
- 80% patients are males
- degenerative calcification of the aortic cups on a substrate of bicuspid aortic valve or rheumatic valve
- Valve myofibroblast differentiates into osteoblast – deposition of calcium hydroxyapatite
- 30% of elderly have valve sclerosis not severe to cause obstruction



Bicuspid Aortic valve



Calcified bicuspid Aortic valve



Degenerated or calcified Aortic valve

Pathophysiology 00:04:38

- not a degenerative wear and tear phenomenon
- active, complex, regulated pathobiological process
  - inflammation
  - lipoprotein deposition
  - RAAS activation
  - osteoblastic transformation
  - active calcification
- Valve myofibroblast differentiates into osteoblast – deposition of calcium hydroxyapatite

Causes of AS 00:06:33

1. Bicuspid valve
2. Rheumatic fever
3. Sclerosed valve

} Calcification

⇒ Young – bicuspid valve

⇒ Elderly – sclerosed valve progressing to calcification

⇒ Overall common cause – sclerosed valve becoming calcified

Genetic polymorphism linked to calcification

- APO ε_4 receptor
- Vitamin D receptor

Active sf

Classification of aortic stenosis 00:08:18

Severity	mean gradient (mmHg)	Aortic valve area (cm^2)
mild	< 25	> 1.5
moderate	25-40	1-1.5
Severe	> 40	< 1
Critical	> 80	< 0.5

- Peak velocity across valve > 4 cm/s ⇒ Severe
- Order of symptoms ASD- Angina, Syncope, Dyspnea

Bicuspid aortic valve 00:10:17

- mc congenital valve defect
- male > female
- Autosomal dominant
- NOTCH 1 defect or endothelial nitric oxide synthase defect
- Complication: aortic dissection
  medial degeneration with ascending aortic aneurysm
- can occur isolated or as a part of shone complex
- mc cause for As in young

Aortic stenosis mimickers 00:12:24

1. Subvalvular stenosis

association with Hypertrophic cardiomyopathy
+
Subvalvular membrane

Symptoms

1. Angina:

Causes for angina in AS

i) LVH (↑ O_2 demand)
ii) ↓ diastolic perfusion time
iii) ↓ capill[redacted]
iv) Atheros[redacted]

Active space

II. Syncope:

due to fixed output state

III. Dyspnea:

Due to – Diastolic failure →Increased LV filling pressure → Increased LA pressure →Increased pulmonary capillary wedge pressure → Dyspnea

- Fixed cardiac output state

⇒ sudden cardiac death may occur in asymptomatic AS individual 0.04%

⇒ sudden cardiac death in symptomatic AS is 1–2 %

Clinical findings

1. Pulse: - normal
   - in severe AS: palpate carotids → Slow rising pulse (pulsus parvus et tardus)
     → Carotid thrill / shudder

2. BP – normal
   - severe AS: narrow pulse pressure

3. JVP – normal

4. Inspection: signs of pulmonary HTN are rare to see

5. Palpation: sustained or heaving apex impulse displaced laterally

Heart sounds

S_1 – normal
- aortic ejection click may be heard

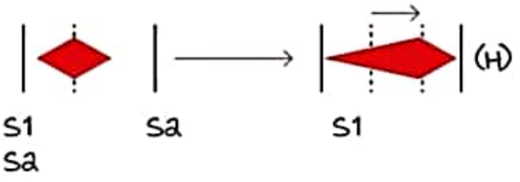
S_2 – soft S_2 (single sound)
- severe AS: Reverse or paradoxically split S_2

S_3 – only in very severe AS (in LV failure)

S_4 – in severe AS

murmur

Physical signs



mild-moderate Severe

- mid-systolic murmur
- Late systolic peaking (in severe as)
- pitch not defined (high + low pitched)
- harsh blowing / rough rasping murmur
- heard with diaphragm on expiration
- aortic area
- ejection systolic click

⇒ Low pitched → Radiates to neck

⇒ High pitch → Radiates to apex (Gallavardin phenomenon)

Severe stenosis indicated by

- slow rising pulse
- narrow pulse pressure
- longer duration of murmur
- S_3, S_4, reverse split, LV heave

II. Supravalvular stenosis

association with William syndrome: Hypercalcemia
Growth failure
mental retardation

Pathophysiology

00:13:08

- due to stenosed valve

↓

- LV outflow obstruction (↑ After load)

↓

- to main cardiac output, pressure induced hypertrophy occurs (concentric LV hypertrophy)

↓

- due to concentric LV hypertrophy:
  - ↑ transvalvular pressure gradient
  - Diastolic dysfunction

    ↓
  - LV diastolic failure

    ↓
  - Contractile dysfunction

    ↓

  ↓ Cardiac output

Clinical features

00:17:30

40/4/1 ⇒ severe AS

> 40 mmHg mean transvalvular gradient

>4 cm/s peak aortic velocity

< 1 cm^2 valve surface area

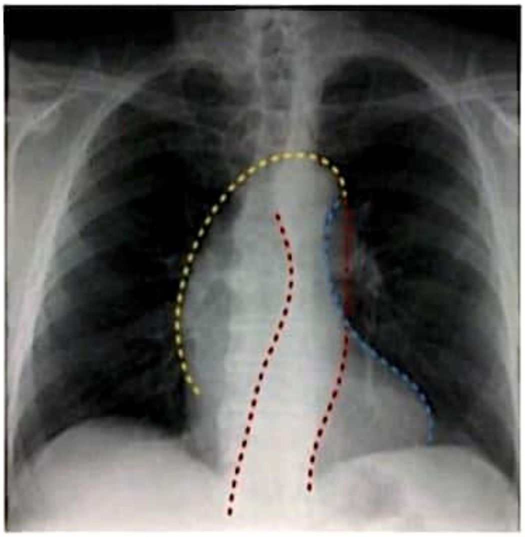
ASD 5/3/2

A-Angina : 5 years ⎫ from the onset of these symptoms
S-Syncope : 3 years ⎬ if patient is not treated then he will
D-Dyspnea : 2 years ⎭ not survive beyond the respective years

ECG

LVH – V1/V2 + V5/V6 > 35mm

X-ray



The ascending aorta (yellow dotted line) leading into the arch is dilated, whereas the distal arch and descending aorta (red dotted line) are normal in size. The left heart border (blue dotted line)

TTE

⇒ severe as: mean aortic flow gradient – > 40 mmHg
Peak systolic aortic velocity – > 4 cm/s
Aortic valve surface area – $< 1\ cm^2$

⇒ sclerosed valve without stenosis;
mean aortic flow gradient: < 25 mmHg
Peak aortic velocity: < 2.5 cm/s

⇒ angiography may be required

⇒ Dobutamine stress ECHO

Low flow low gradient severe AS(true severe AS) (stroke volume < 35 ml/min and gradient < 40 mmHg) and LV failure (pseudo severe AS) can be differentiated with dobutamine stress Echo

Cardiac catheterization

- multivavular heart disease
- Young congenital noncalcific asymptomatic AS who may benefit from percutaneous aortic ballon valvotomy (PABV)
- Subvalvular or supravalvular AS

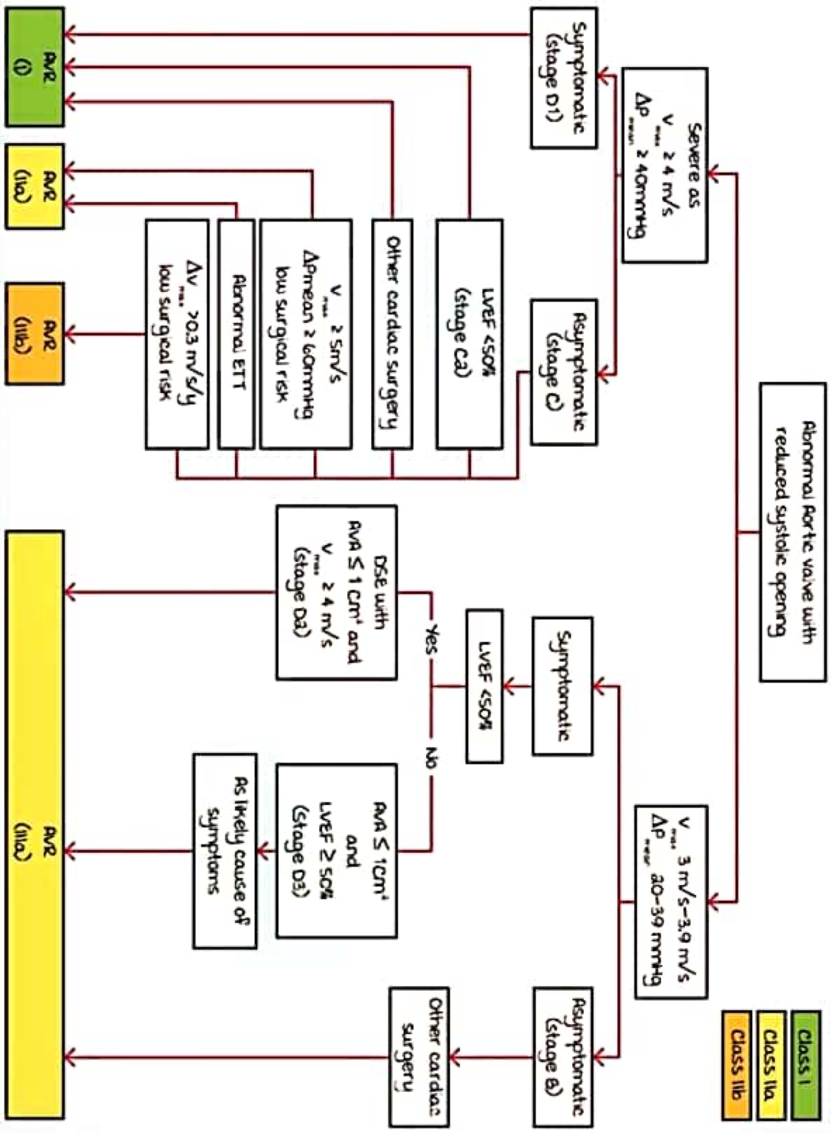
Treatment

Surgery

- Aortic valve replacement (AVR)
- Transcatheter aortic valve implantation (TAVI)
- Percutaneous Ballon aortic valvotomy (PBAV) – for congenital AS or patients with comorbidities

AVR in AS

- symptomatic AS
- asymptomatic with LVEF <50%
- rapid progression on yearly ECHO
- symptomatic on Dobutamine stress test
- young patient with bicuspid aortic valve


Abnormal Aortic valve with reduced systolic opening
Severe AS $V_{max} \geq 4$ m/s $\Delta P_{mean} \geq 40$mmHg
V_{max} 3 m/s–3.9 m/s ΔP_{mean} 20–39 mmHg
Symptomatic (stage D1)
Asymptomatic (stage C)
LVEF <50% (stage C2)
Other cardiac surgery
$V_{max} \geq 5$m/s ΔPmean ≥ 60mmHg low surgical risk
Abnormal ETT
ΔV_{max} >0.3 m/s/y low surgical risk
Symptomatic
LVEF <50%
Yes
No
DSE with AVA ≤ 1 cm² and $V_{max} \geq 4$ m/s (stage D2)
AVA ≤ 1cm² and LVEF ≥ 50% (stage D3)
AS likely cause of symptoms
Asymptomatic (stage B)
Other cardiac surgery
AVR (I)
AVR (IIa)
AVR (IIb)
AVR (IIa)
Class I
Class IIa
Class IIb

AORTIC REGURGITATION

Classification and causes

00:00:08

1. Acute AR

2. Chronic AR

A) Valvular disease causing AR:
- Rheumatic AR (mc cause)
- Congenital AR
- Infective endocarditis
- Ankylosing spondylitis
- Syphilis

B) Aortic root dilatation causing AR
- Marfan syndrome
- Aortic dissection
- Bicuspid aortic valve
- Takayasu arteritis

⇒ Rheumatic disease cause AR by

1. Annular dilation
2. Chronic inflammation causing thickening, deformity and shortening of aortic valve cusp

Pathophysiological mechanism in AR

00:02:42

During diastole there is regurgitant blood from aorta to LV

↓

↑ LV end diastolic volume

↓

LV increase in size

↓

LV undergo eccentric hypertrophy

↓

LV dilatation ↑ the LV systolic wall stress required to develop any level of systolic pressure

↓

↑ in stroke volume

↓

↑ cardiac output

Active space

- Thus preload and afterload increases
- Increased stroke volume results in abrupt distention of peripheral arteries and increased systolic BP
- Regurgitation back into LV from peripheral arteries leads to rapid fall in pressure with quick collapse of arteries and a diastolic BP that can touch zero
- Since there is ↑ SBP and ↓ DBP, there is widening of pulse pressure
- Patient remains asymptomatic for decades
- Palpitations due to ↑ LV size
- Exertional dyspnea only when there is LV systolic dysfunction
- Nocturnal angina due to fall in arterial diastolic pressures and ↑ regurgitant volume reducing coronary perfusion

⇒ There is serve AR when there is widening of pulse pressure

Clinical findings

00:09:29

1. Traube's sign: Pistol shot sounds
   Booming systolic and diastolic sounds heard over the femoral arteries

2. muller's sign: Systolic pulsations of uvula

3. Duroziez sign: Systolic murmur over the femoral artery when compressed proximally and diastolic murmur when compressed distally

4. Quincke sign: Increased capillary pulsations in the nail bed, lips & finger tips is called Quincke's sign

   Capillary pulsations detected by
   - Pressing a glass slide on the lips
   - Transmitting a light through the patient's finger tips
   - Exerting gentle pressure on the tip of finger nail

5. De musset sign: nodding of head with each heart beat

6. Hill sign: Popliteal cuff systolic pressure exceeding brachial cuff systolic pressure by more than 20 mmHg

7. Corrigan's pulse: Water hammer pulse
seen in severe AR; AS + AR (moderate)

8. Becker's sign: Retinal pulsation

9. Rosenbachs sign: Seen in liver

10. Gerhard's sign: Spleen

The above findings occurs due to wide pulse pressure

Apex:

Down and out hyperdynamic forceful apex

Heart sounds

S_1 – Soft due to premature closure

S_2 – A2 soft or absent

S_3 – Heard when there is LV systolic failure

S_4 – Not heard

Symptoms

- Asymptomatic for 10 years
- Palpitations on lying down / sinus tachycardia on exertion or emotion
- Dyspnea
- Angina with flushing due to reduced coronary flow due to diastolic hypotension

Murmur 00:14:00

1. Early diastolic murmur:

- High pitched,soft blowing decrescend murmur
- Best heard in the 3rd left intercostal space- Neo aortic area
  - With the patient sitting up and leaning forward
  - Breath held in forced expiration
- Aortic root disorders – murmur is heard along right sternal border
- Cooving or musical murmur – Evertion or perforation of aortic cusps

Active space

⇒ Longer the duration of murmur serve the AR

⇒ Becomes short in cardiac failure

II. Ejection systolic murmur

- Flow murmur
- Best heard at the base of the heart
- Transmitted along the carotids

III. Austin flint murmur

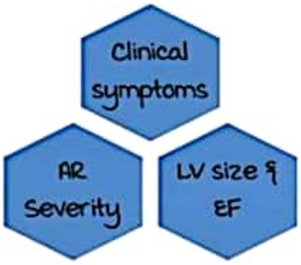
- Soft, low pitched rumbling mid diastolic murmur
- Diastolic replacement of the anterior leaflet of the mitral valve by the aortic regurgitant stream
- Auscultatory events – intensified by handgrip

Warning : Not all points are covered in the notes, especially conceptual explanations. Please use the notes in conjunction with Marrow Edition 4 videos.

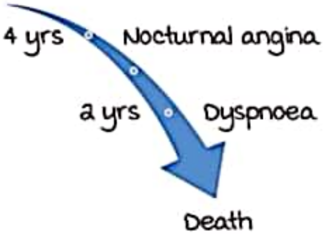
Assessment of AR

00:17:41

- Factors determining the timing of Sx



- Natural history in presurgical era



Transthoracic echo with Doppler for severe AR

- Central jet width > 65% of LVO tract
- Vena contracta width > 6 mm
- Regurgitant fraction > 50%
- Regurgitant volume > 60 ml / beat
- Effective regurgitant orifice area < 0.3 cm²

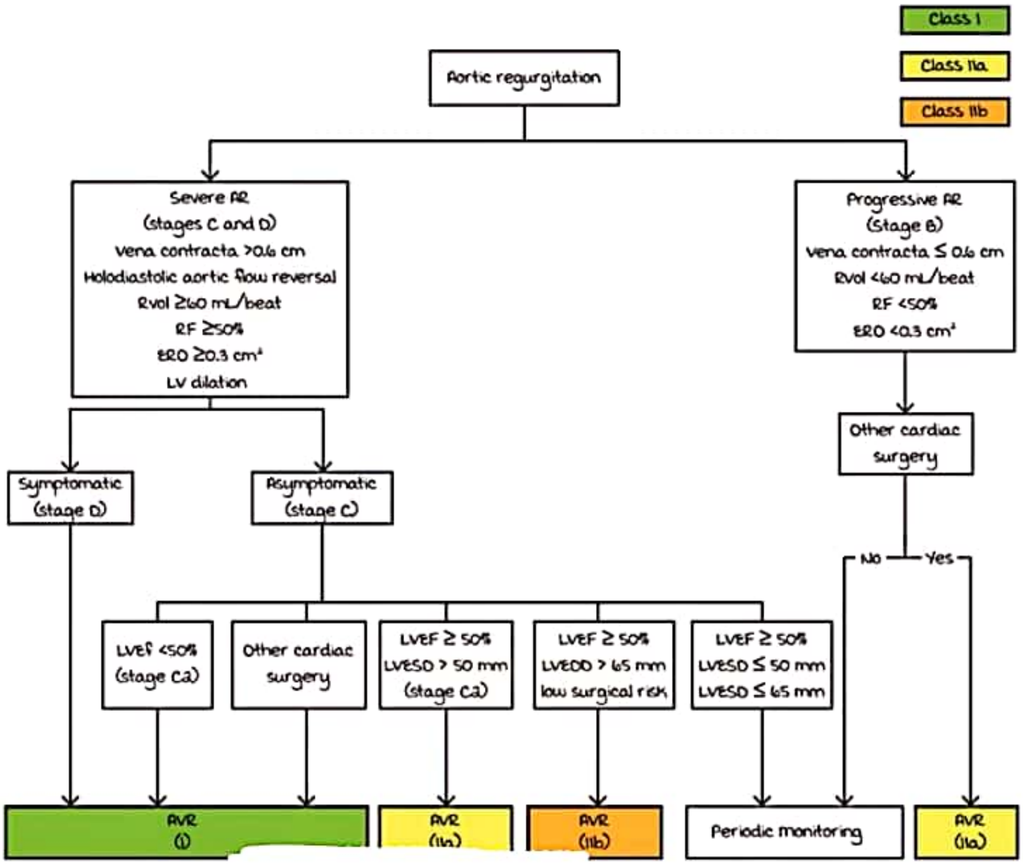
Management

00:19:10

- Severe AR and symptomatic – Aortic valve replacement

- Severe AR and asymptomatic

  Indication for surgery:
  - LV EF is <50%
  - Other cardiac surgery
  - LV end systolic diameter >50 mm
  - LV end diastolic diameter >65 mm


Class I
Class IIa
Class IIb
Aortic regurgitation
Severe AR (stages C and D) Vena contracta >0.6 cm Holodiastolic aortic flow reversal RVol ≥60 mL/beat RF ≥50% ERO ≥0.3 cm² LV dilation
Progressive AR (Stage B) Vena contracta ≤0.6 cm RVol <60 mL/beat RF <50% ERO <0.3 cm²
Symptomatic (stage D)
Asymptomatic (stage C)
Other cardiac surgery
No
Yes
LVEF <50% (stage C2)
Other cardiac surgery
LVEF ≥ 50% LVESD > 50 mm (stage C2)
LVEF ≥ 50% LVEDD > 65 mm low surgical risk
LVEF ≥ 50% LVESD ≤ 50 mm LVEDD ≤ 65 mm
AVR (I)
AVR (IIa)
AVR (IIb)
Periodic monitoring
AVR (IIa)

Aortic regurgitation: Intervention

Recommendations	COR	LOE
AVR is indicated for symptomatic patients with severe AR regardless of LV systolic function (stage D)	1	B
AVR is indicated for asymptomatic patients with chronic severe AR and LV systolic dysfuction (LVEF <50%) (stage C2)	1	B
AVR is indicated for patients with severe AR (stage C or D) who are undergoing other cardiac surgery	1	C

Aortic Regurgitation: Intervention (cont.)

Recommendations	COR	LOE
AVR is reasonable for asymptomatic patients with severe AR with normal LV systolic function (LVEF ≥50%), but severe LV dilation (stage C2, LVESD > 50 mm)	IIa	B
AVR is reasonable in patients with moderate AR (stage B) who are undergoing other cardiac surgery	IIa	C
AVR may be considered for asymptomatic patients with severe AR and normal LV systolic LV systolic function (stage C1, LVEF ≥ 50%)but severe LV dilation (LVEDD > 65mm) if surgical risk is low*	IIb	C

RESTRICTIVE AND DILATED CARDIOMYOPATHY

98

Definition 00:00:08

Cardiomyopathy is a myocardial disorder in which heart is structurally and functionally abnormal in the absence of CAD, valvular heart diseases, hypertension and congenital heart disease

Types:

1. Dilated cardiomyopathy
2. Hypertrophic cardiomyopathy
3. Restrictive cardiomyopathy

Restrictive cardiomyopathy 00:02:18

- There is restriction to filling of left and right ventricle
- In restrictive cardiomyopathy
  1. There is severe diastolic dysfunction (heart unable to receive enough blood during diastole)
  2. Systolic function almost normal (EF preserved till late)
  3. Both atria are massively enlarged with LV dimension near normal
  4. High end diastolic pressure (EDP)
- Causes
  1. Infiltration between myocytes
  2. Storage of a substance within myocytes
  3. Fibrosis

1.Infiltration between myocytes

a. Amyloidosis:

- most common cause of restrictive cardiomyopathy
- Seen most commonly in Familial amyloid polyneuropathy (due to transthyretin mutation)
- Also seen in senile systemic amyloidosis, primary amyloidosis

Note: Secondary Amyloidosis → Kidney is maximally affected and heart is generally spared

b. Sarcoidosis

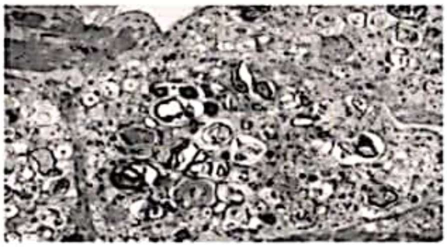
Active space

II. Storage within myocytes

most often due to metabolic defects

a. Fabry's disease:

- Due to α-galactosidase deficiency
- Concentric lamellar inclusions



b. Glycogen storage disease type III- due to debranching enzyme defect

c. Hemochromatosis

- Due to iron deposition
- Note: Dilated cardiomyopathy is more common in hemochromatosis than restrictive cardiomyopathy

III. Fibrosis of myocardium

a. Scleroderma

b. Endomyocardial fibrosis

1. Tropical endomyocardial fibrosis: - Hypereosinophilia
   - Loeffler's syndrome (Ascaris)
2. Carcinoid syndrome
3. Radiation
4. Ergotamine, serotonin

Clinical findings

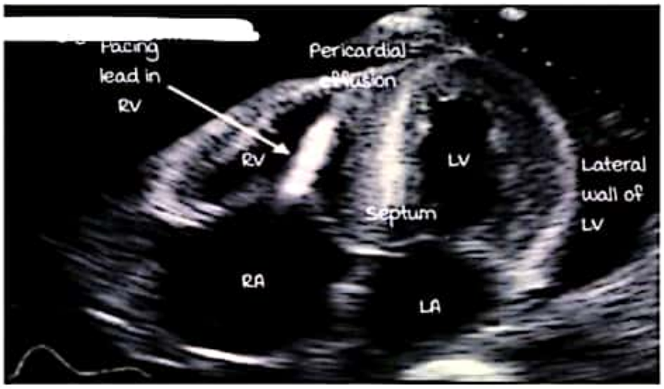
- mostly asymptomatic
- Subtle exercise intolerance is the earliest symptom
- Always predominant right sided symptoms
- Left sided congestive symptom due to ↑ EDP occur very late
- Apex not so displaced as in dilated cardiomyopathy nor so hyperdynamic as in HOCM
- S_4 is heard

Restrictive cardiomyopathy vs constrictive pericarditis 00:17:07

Restrictive Cardiomyopathy	Constrictive Pericarditis
• History of amyloidosis sarcoidisis	• History of TB
• Elevated JVP: x- descent	• Elevated JVP: x and y descent
• Kussmaul sign +	• Kussmaul sign ++
• Congestive symptoms are more common	• Congestive symptoms are less common
• S_3 and S_4 heard	• Pericardial knock +
• Repolarization abnormalities, LVH & q-wave in ECG	• Low voltage complexes • Equalization of diastolic pressure

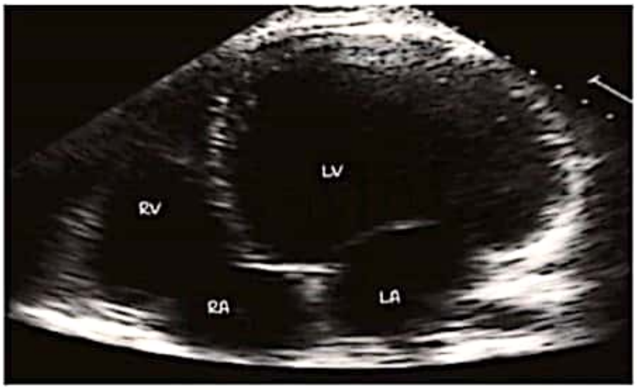
Restrictive cardiomyopathy in amyloidosis 00:19:52

- Amyloidosis is the most common cause of restrictive cardiomyopathy
- Thickened ventricular wall (Generally in restrictive cardiomyopathy wall thickness is near normal)
- Low voltage ECG complexes (It is more commonly seen in constrictive pericarditis, but restrictive cardiomyopathy due to amyloidosis has low voltage ECG complexes
- Hyper refractile glittering of myocardium
- Dilatation of both atria
- Poor prognosis



Dilated cardiomyopathy 00:23:00

- MC type of cardiomyopathy
- In dilated cardiomyopathy
  - LV thinning
  - LV is dilated
  - Cardiomegaly
  - LV systolic dysfunction
  - Systolic heart failure



- Left ventricle is more involved than right ventricle
- Dilated cardiomyopathy result in LV systolic heart failure

Note:

The term ischemic cardiomyopathy is not used because cardiomyopathy is defined in the absence of CAD (ie., Ischaemia)

Causes of dilated cardiomyopathy 00:27:30

I. Genetic causes

- 70% are genetic
- MC genetic cause is titin gene mutation (AD)
- Desmosomal mutation (AR): It produces arrhythmogenic right ventricular dysplasia (ARVD)
- Tafazzin mutation (x-linked recessive): It produecs LV non-compaction

II. Myocarditis

- Infective myocarditis
- Non- infective granulomatous myocarditis

III. Drug induced cardiomyopathy

IV. Peripartum cardiomyopathy

V. Alcoholic cardiomyopathy

Clinical features 00:31:17

- Due to LV systolic failure predominant findings will be due to ↓ cardiac output
- MC is fatigue/dyspnea (initially on exertion later at rest)
- Due to biventricular dilatation → Congestion symptoms (edema, orthopnea, rise in JVP)
- Due to ↓ cardiac output → It can cause hypoperfusion
  - Cold extremities
  - Neurological abnormalities
  - Renal hypoperfusion
  - Cachexia – weight loss
  - Hypotension

Clinical signs

- JVP elevated
- Cardiomegaly
- Apex – Displaced down and out
- S_3
- Pulsus alterans
- Edema / ascites
- ECG: Non-specific ST-T changes, sometimes 'q' waves

Complications

1. Arrhythmia
2. Thromboembolic events
3. Acute decompensated heart failure

Active space

	Idiopathic dilated cardiomyopathy (DCM)	Ischemic dilated cardiomyopathy(IDCM)
Past history of CAD	Should be absent	Present in most
Antecedent fever, systemic illness	may be present	Not relevant
Symptoms	Angina uncommon	Angina may be present
ECG (Q waves, LBBB, low voltage QRS, slurred, notched QRS, Fascicular blocks, Non specific ST/T changes)	Generally not usefull. Q waves are more common in IDCM. Diffuse q waves not confining to an arterial territory may suggest idiopathic DCM Please remember q waves are not synonymous with infarct. It can occur with scars, fibrosis, extreme atrial enlargement (Cavity potential)	
X ray chest	Global Cardiomegaly	more of LV configuration
ECHO	4 chamber dilatation Common (Can be made as essential criteria)	LV, LA dilatation predominant
Wall motion defect	Uniform Global hypokinesia	Global hypokinesia with regional variation
myocardial scars	Less common (more of shinning)	Significant scars, Random and patchy.(makes CRT difficult)
mitral regurgitation	Usually present (Central jet)	Often present (Eccentric jet common due to differential pap muscle involvement)
Diastolic dysfunction	Often restrictive	Grade I or 2 (Rarely restrictive)
RV dysfunction (RVD)	High incidence (True myopathies do not differentiate RV and LV)	Less common (RVD is due to spiral muscle sharing between RV and LV)

Myocarditis

00:40:18

Causes

I. Infective myocarditis

- Chagas disease (MC cause of myocarditis)
- Lyme disease

II. Non- Infective myocarditis

- Granulomatous inflammatory disease
  - Sarcoidosis (MC cause of non-infective myocarditis)
  - Giant cell myocarditis

TABLE 254-4 Major Causes of Dilated Cardiomyopathy (with Common examples)

Inflammatory myocarditis

- Infective
  - Viral (coxsackie, adenovirus, HIV, hepatitis C)
  - Parasitic (T. cruzi-chagas disease, trypanosomiasis, toxoplasmosis)
  - Bacterial (diphtheria)
  - Spirochetal (Borrelia burgdorferi-Lyme disease)
  - Rickettsial (Q fever)
  - Fungal (with systemic infection)
- Noninfective
  - Granulomatous inflammatory disease
  - sarcoidosis
  - Giant cell myocarditis
  - Eosinophilic myocarditis
  - Polymyositis, dermatomyositis
  - Collagen vascular disease
  - Checkpoint inhibitor chemotherapy
  - Transplant rejection

myocarditis

- Any systemic infection with severe cytokine release can depress LV function
- At the time of viral illness or during recovery from the illness if the patient presents with following consider as myocarditis

i. Acute Coronary syndrome like presentation with global LV dysfunction with Troponin I elevation + ECG showing ST-T changes

ii. Patient develops new onset heart failure

- It can lead to complication like cardiogenic shock/ arrhythmias
- No specific therapy for myocarditis
- Global hypokinesia without regional variation

Dallas criteria: Histological criteria for myocarditis

- MC non-infective cause is sarcoidosis
- MC cause of death in churg - strauss syndrome is: Cardiac cause (myocarditis)
- Giant cell myocarditis with rapidly progressive heart failure

Peripartum cardiomyopathy 00:48:23

- Good prognosis
- Risk of recurrence = 30 - 40%
- Seen in last trimester or first 6 months after pregnancy

- Pathological factor: Anti-angiogenic or Anti-VEGF ie SFLT,
- Present as LV systolic failure + EF<40%
- major risk factors are – Age at pregnancy + Hypertension
- No specific therapy

Drug induced cardiomyopathy 00:50:13

- Worst prognosis

Drugs

- Anthracyclines – Ex: Doxorubicin, daunorubicin, mitoxantrone
- Trastuzumab
- Cyclophosphamide
- VEGF inhibitors – Bevacizumab
- Proteasome inhibitors – Bortezomib

Alcohol induced cardiomyopathy 00:52:01

- Reversible after cessation of drinking
- Asymptomatic
- There is risk for atrial fibrillation (Holiday heart syndrome)
- Acetaldehyde is dangerous molecule
- ACE polymorphism are most susceptible

Rare causes of dilated cardiomyopathy 00:53:15

Toxic
Alcohol
Catecholamines: amphetamines, cocaine
Chemotherapeutic agents (anthracyclines, trastuzumab)
Interferon
Other therapeutic agents (hydroxychloroquine, chloroquine)
Drugs of misuse (emetine, anabolic steroids)
Heavy metals: lead, mercury
Occupational exposure: hydrocarbons, arsenicals
Metabolic
Nutritional deficiencies: thiamine, selenium, carnitine
Electrolyte deficiencies: calcium, phosphate, magnesium
Endocrinopathy
thyroid disease
Pheochromocytoma
Diabetes
Obesity
Hemochromatosis

Management of dilated cardiomyopathy is like managing LV systolic heart failure

Hypertrophic Cardiomyopathy

Definition and pathophysiology

00:00:32

In hypertrophic cardiomyopathy there is

- Severe LV hypertrophy without dilatation:
  - No other possible cause of LVH
  - Septal > free wall freewall hypertrophy
  - Assymetrical hypertrophy (LV > RV)
  - Due to this there is diastolic dysfunction, and systolic function is preserved till late in the disease

- LV outflow tract obstruction:
  - It occurs due to septal hypertrophy and
  - SAM = systolic motion of anterior mitral leaflet

- Due to SAM → LV outflow obstruction → MR

- Coronary vessels are stiff and intramural occlusion
  Hence patient can develop silent myocardial ischemia

- Due to hypertrophy, patient is prone to develop arrhythmias

Note:

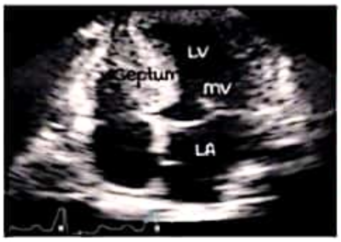
1. The pathological finding is myofiber disarray
2. Average age diagnosed is 40 years
3. 98–99% have stable course
4. Only 1–2% will have worsening
5. It is a genetic condition – Autosomal dominant
6. Sarcomere gene mutation most commonly involves–β–myosin heavy chain
7. Females = males. Females have more progressive disease

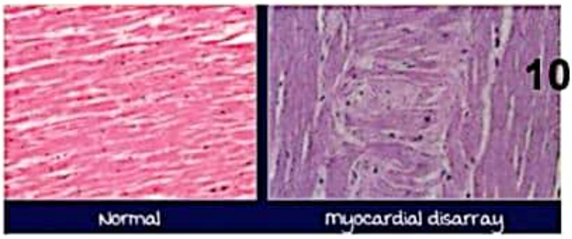
Other names

- Asymmetrical septal hypertrophy (ASH)
- Idiopathic hypertrophic subaortic stenosis (IHSS)
- HOCM

Active space

- In Japanese there is ap





Pathophysiology

00:08:04

Complex and consists of multiple interrelated abnormalities

1. Diastolic dysfunction
2. LVO tract obstruction
3. mitral regurgitation
4. myocardial ischemia
5. Arrhythmias

I. Diastolic dysfunction

- 80%
- LV hypertrophy
- Replacement scarring and interstitial fibrosis and disorganized cellular architecture
- Diastolic dysfunction is likely to be the fundamental mechanism by which heart failure occurs in nonobstructive HCM with preserved LV systolic function
- Earliest symptom is subtle exercise intolerance

II. Left ventricular outflow tract obstruction:

- Mechanism of obstruction is multifactorial
- Dynamic obstruction mostly due to SAM
- Increased myocardial contractility, decreased ventricular volume or decreased afterload increase the degree of subaortic obstruction

⇒ LVO tract obstruction is due to

- Systolic anterior motion of mitral value leaflet (SAM) +
- Septum hypertrophy

⇒ LVO tract obstruction is determined by

- i) LV cavity size (preload)
- ii) Force of contraction
- iii) Afterload

i) Preload

When there is decrease in preload (For example due to diuretics, hypovolemia, nitrate etc)

↓

LV cavity size reduces → more severe obstruction

- This leads to ↑ in intensity of murmur
- Hence dehydration, diuretic, nitrate are contraindicated in HCM

2) Force of contraction

- Increase force of contraction will worsen the obstruction and intensity of murmur increases
- Digoxin is contraindicated in HCM
- Exercise, tachycardia are bad in HCM

3) Afterload

- Decrease in afterload will increase in obstruction

Note:

⇒ Valsalva manoeuvre and standing ⇒ Increase in intensity of murur in MVP and HCM (due to ↓ preload)

⇒ Squatting and leg raising ⇒ Decrease in intensity of murmur of HCM (due to ↑ preload)

⇒ Isotonic handgrip ⇒ Decrease in intensity of murmur of HCM - Due to ↑ peripheral resistance

SAM

- LV ejection produces a high velocity jet, which streams through a narrowed outflow tract, pulling the mitral leaflets towards the septum

III. Mitral regurgitation

- MR, as a consequence of SAM is posteriorly directed and is usually only mild to moderate in degree

- Severe MR in HCM raises the possibility of an intrinsic mitral valve abnormality, such as myxomatous degeneration with mitral valve prolapse

IV. Myocardial ischemia

- It is due to intramural coronary occlusion

Clinical features

00:18:56

- Asymptomatic
- Due to LV diastolic failure

↓

Subtle exercise intolerance (MC symptom)

↓

Dyspnea on exertion (due to ↑ LV filling pressure)

↓

Angina (due to coronary vascular change) + LVH (which ↑ O_2 demand)

↓

Orthopnea + PND (due to ↑ LV filling pressure)

↓

↓ cardiac output → Syncope, fatigue

- Symptoms are not proportional to degree of obstruction
- Pulsus bisferiens → Seen in AR, AR+AS, HOCM
- Apex:
  - Sustained apex, down, (no cardiomegaly)
  - Double or triple apical impulse

↓

↑ Flow across obstruction → SAM (worsen obstruction) → Across SAM → Presystolic accentuation

Heart sounds: S_1 → Normal

S_2 → Single S_2 (P_2) or Paradoxical Split of S_2

S_3++: S_4++

- Murmur:
  - Medium pitched murmur
  - Ejection systolic murmur
  - Best heard at apex / lower left sternal border

Active space

- No radiation to carotids
- Increase on dynamic auscultation ie ↑ in intensity on standing, valsalva, exerxise

- ECG: 90% LVH
  ST-T changes

- In apical hypertrophic cardiomyopathy (a.k.a yamaguchi disease) Giant T wave inversions waves are seen [seen in Jan penses]

- Echocardiography
  - Gold standard for the diagnosis of HCM
  - Finding of increased wall thickness in the absence of another etiology is the basis for the diagnosis of HCM
  - Hypertrophy can be distributed throughout the myocardium in any pattern but commonly involves the entire ventricular septum

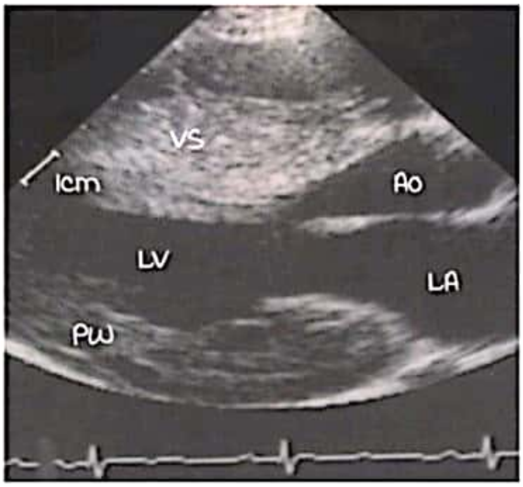
⇒ Average maximal left ventricular wall thickness in a population of HCM patient is usually 20 to 22mm

⇒ 5 to 10% of patients have maximal wall thickness in excess of 30 mm

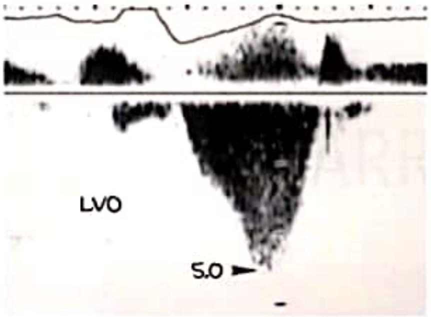
⇒ If true dynamic obstruction is present there is SAM of the mitral valve apparatus

⇒ Exact site of the obstruction may be determined by visualizing the region of the SAM-septal contact

- In the classic form – Obstruction occurs at the most basal portion of the septum as it projects into LVO tract



- Continous Doppler wave sonography
  - Done to look for LV outflow tract
  - Dagger shaped signal



Natural history

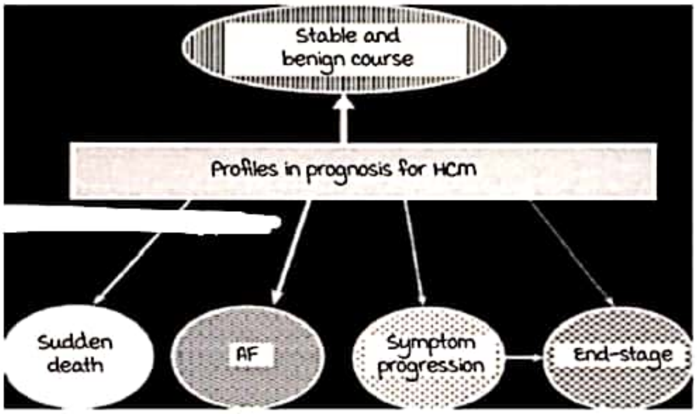
00:28:54

- Present at any age
- Risk of sudden cardiac death
- Patients with HCM remain stable during long period
- Adults with HCM have the same overall life expectancy as that of an age and sex matched general population

Rarely it can lead to

1. Sudden and unexpected death
2. Progressive heart failure with exertional dyspnea and functional limitation (often accompanied by chest pain) in presence of preserved LV systolic function
3. Atrial fibrillation with the risk for embolic stroke and heart failure

Natural history


Stable and benign course
Profiles in prognosis for HCM
Sudden death
AF
Symptom progression
End-stage

Sudden cardiac death (SCD) in HCM 00:31:06

- Death can be sudden, unexpected and may be the first manifestation of HCM, particularly in the young patients
- SCD usually occurs in patients who have no or mild symptoms
- SCD is most frequent in young adults (< 30-35 years) but may also occur in the older populations
- A substantial proportion of patients die during or just after vigorous physical activity

Risk factors for SCD in HCM

⇒ major risk factors

- Cardiac arrest (ventricular fibrillation)
- Spontaneous sustained ventricular tachycardia
- Family history of sudden death

⇒ minor risk factors

- unexplained syncope
- Left ventricular wall thickness > 30 mm
- Abnormal BP on exercise
- Nonsustained ventricular tachycardia
- Left ventricular Outflow tract obstruction
- microvascular obstruction
- High-risk genetic defect

⇒ 1 major risk factor or ≥ 3 minor risk factor is an indication for Implantable Cardiac Defibrillator

Management 00:33:56

- All HCM patients should be counseled against engaging in competitive athletics
- Low to moderate levels of aerobic exercise are permitted as a part of a healthy lifestyle
- Patient with a dynamic Left ventricle Outflow tract obstruction should be given infective endocarditis prophylaxis
- Patients should be instructed to maintain hydration at all times

medical therapy

I. Beta blockers

Initial drug of choice

Advantage i) Decreased heart rate response to exercise
ii) Decreased outflow tract gradient with exercise
iii) Relief of angina by a decrease in myocardial O_a demand
iv) Improvement in diastolic filling

Drugs – Atenolol
metoprolol
Propranolol: Start at a mg/kg/day to 480 mg/day to achieve heart rate of 60 bpm

II. Calcium channel blocker

- used in patients who are intolerant to beta blocker
- Verapamil: Improve diastolic filling
  Improve exercise tolerance
  Relief of angina
- DHP (dihydropyridine) are never used

III. Disopyramide

- If symptoms are still present inspite of β – blocker or CCB add disopyramide (Na = Channel blocker – Class Ia anti-arrhythmic drugs)
- It reduces Dp/dt of phase 1
- Adverse effect: QT– prolongation

Drug	Resting gradient reduction	Exercise gradient reduction	Improvement in diastolic function
Beta blocker	+	+++	+
Verapamil	+	+++	++
Disopyramide	++	+++	+

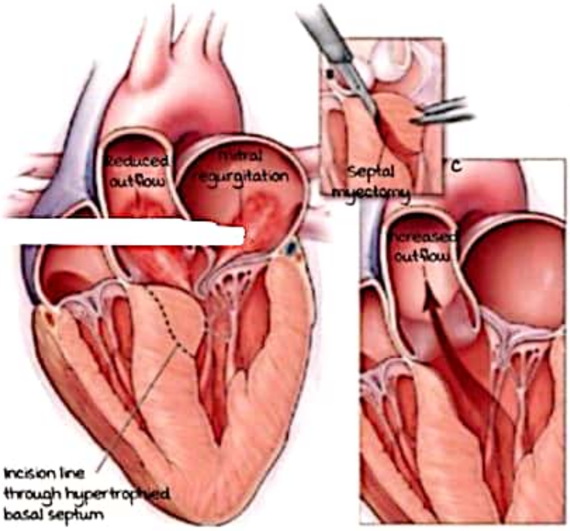
Non-pharmacological therapy

- For drug refractory or drug intolerant patients
- useful only in patients with resting gradient 30 mmHg or provocable gradient 50 mmHg and in patients with h/o exertional syncope

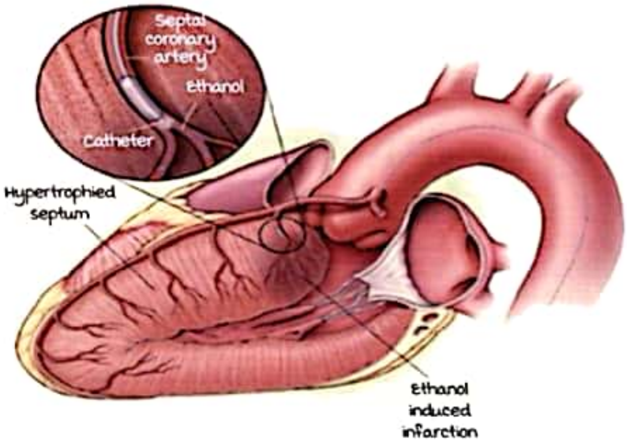
3 interventions

1. Septal myectomy
    - Gold standard therapy for patient with obstruction and severe drug refractory symptoms
    - Immediate relief
    - Improvement in >70% of patient
    - Less risk

Septal myectomy


Reduced outflow
Mitral regurgitation
Septal myectomy
C
ncreased outflow
Incision line through hypertrophied basal septum

Septal ablation


Septal coronary artery
Ethanol
Catheter
Hypertrophied septum
Ethanol induced infarction

2. Alcohol septal ablation Done if patient is not fit for surgery
3. Dual chamber pacing

Dual chamber pacing

- Less invasive therapeutic modality for treatment of symptomatic HCM patients
- Pacing the right ventricular apex in a subset of patients can decrease the outflow tract gradient, presumably because of ventricular contraction alteration with a decrease in systolic projection of the basal septum into the aeft Ventricular Outflow tract
- Chronic remodelling effect during continuous pacing with enlargement of the left ventricular cavity and further decrease in outflow tract obstruction

Table 3. Comparative Features of Septal-Reduction therapies

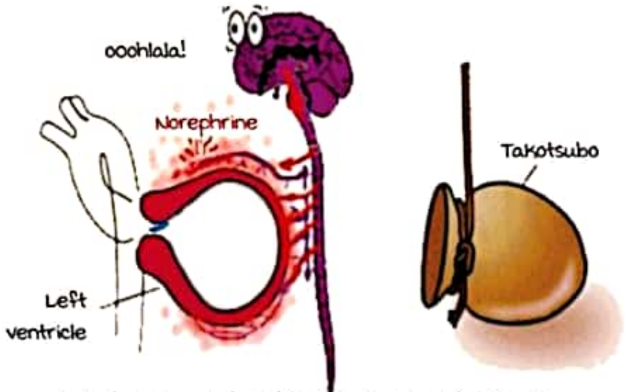
Therapy	mortality	Residual gradient	Effectiveness	Follow-up	Complications		Time to Resolution of gradient
	%	mmHg	% of patients	Yr	Type	% of patients	
Dual-chamber pacing	<1	<40	10-40	10	Infection or perforation	<2	4 wk
Septal myectomy*	<2-3	<10	<90	>30	Complete heart block	<3	Intermediate
					Ventricular septal defect	<1	
					Aortic regurgitation	<1	
Septal ablation	<2-3	<20	70-80	<5	Complete heart block	10-40	8-12 wk
					Ventricular septal defect	unknown	
					Large myocardial infarction	unknown	

Arrhythmogenic Right Ventricular Dysplasia (ARVD) 42:04

- myocardium of RV free wall replaced by fibrofatty tissue
- RV function abnormality with regional akinesia progressing to RV dysfunction
- Mutation in desmosomal genes

Takotsubo cardiomyopathy 00:43:15

- Also called LV apical ballooning or stress induced cardiomyopathy
- middle aged females
- Transient regional systolic dysfunction of LV mimicking MI with normal angiogram
- Global ventricular dilatation with basal contraction (apical type)
- Good prognosis



Catecholamine-induced transient myocardial stunning

- Female > male
- Trigger +
- Chest pain + dyspnea
- Arrhythmia/shock rarely
- ST elevation + troponin I elevation
- Clinical manifestation and ECG findings are disproportionate to troponin I elevation

DCM vs RCM/ vs HCM

00:46:03

Features	Dilated cardiomyopathy	Restrictive cardiomyopathy	Hypertrophic cardiomyopathy
1. Character-ized By	• LV Thinning • LV systolic dysfunction • EF <30%	• Right side involvement • Diastolic dysfunction • EF 40-50% (many times normal)	• Left side involvement • Diastolic dysfunction • EF normal
2. Ventricular size	Dilated	• Normal size • Atria size ↑ • Thickness ↑ in amyloidosis	Normal size (thickness ↑)
3. Secondary MR	Present (due to annular dilatation)	Present (due to endocardial involvement)	Present (due to SAM)
4. Earliest symptoms	Dyspneal fatigue (left sided symptoms)	Exertional intolerance (right sided symptoms)	Exertional intolerance (left sided symptoms)

Active space

ACUTE HEART FAILURE

Types of heart failure 00:00:12

1. Acute heart failure
2. Chronic heart failure ⇒ a) Heart failure with reduced EF (<40%)
   b) Heart failure with preserved EF (>50%)

Acute heart failure 00:01:17

1. Also Known as Acute Decompensated Heart Failure (ADHF)
2. 80% of acute heart failure are due to worsening of chronic heart failure (underlying structural heart disease)
   - Anaemia
   - Causes that leads to worsening of heart failure :
   - Infective endocarditis
   - Renal failure
   - Drugs
3. 20% can be due to denovo acute heart failure

Types of Acute Decompensated Heart Failure (ADHF) 00:02:45

1. mild to moderate ADHF 70% mild to moderate ADHF → most common
2. Hypertensive ADHF
3. Pulmonary edema
4. Cardiogenic shock

1. mild to moderate ADHF

- 70% have underlying structural heart disease
- No cardiogenic shock
- No hypertensive crisis
- No pulmonary edema
- There is slight volume overload
- Progressive dyspnea
- Abdominal pain
- Peripheral congestion

- ↑ JVP
- Tender enlarged liver
- Pedal edema
- Underlying systolic HF shows: S_3
  Cardiomegaly
  MR

II. Hypertensive ADHF

- Seen in 10-15% of patients
- Older women
- Patients mostly have diastolic heart failure due to systemic hypertension and hypertension is poorly controlled
- Patient will be having symptoms of elevated filling pressure which result in acute onset dyspnea
- Preserved LVEF

III. ADHF with pulmonary edema

ADHF with ↑ filling pressure
↓
↑ pulmonary venous pressure
↓
Pulmonary edema

- Suffocation and air hunger
- Tachypnea, tachycardia, elevated BP
- Sweating +++
- Fine crepitations at lung base

iv. Cardiogenic shock

- SBP < 90 mmHg
- Signs of decreased end organ perfusion
  - Fatigue
  - Altered mentation
  - Cyanosis
  - Cool extremities
  - Pre renal failure
  - Narrow pulse pressure
  - Pulsus alternans

Causes for acute pulmonary edema 00:09:49

1. Cardiac causes
   - Worsening of underlying structural heart disease
   - Heart failure with reduce EF
   - Chronic valvular heart disease
   - Cardiomyopathy

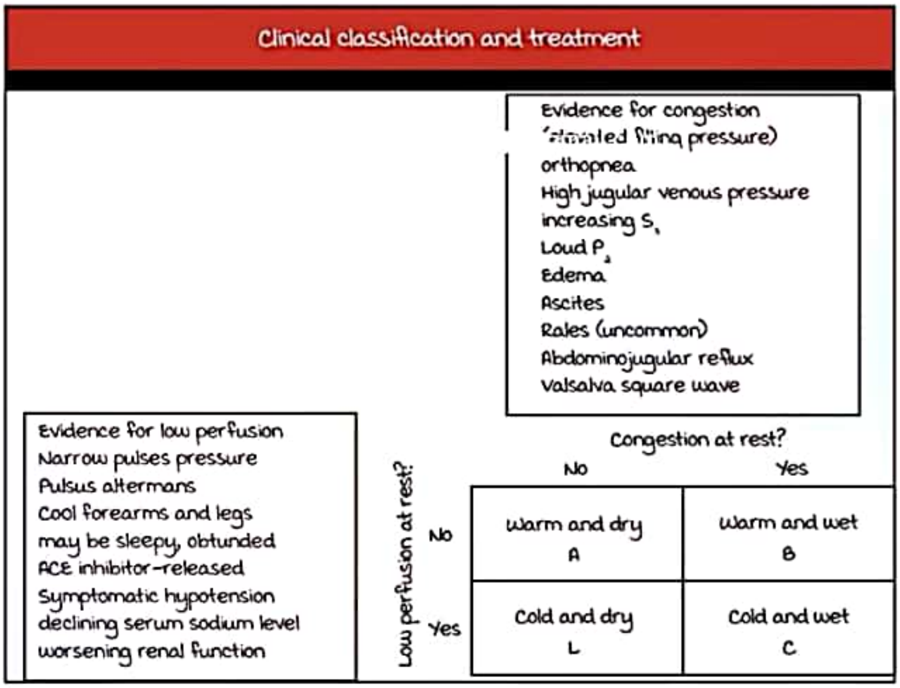
2. Renal

De novo ADHF in pulmonary edema 00:10:41

1. Cardiac
   - most common cause
   - Ventricular septal rupture
   - Acute AR or Acute MR
   - myocarditis
   - Cardiomyopathy

2. Renal
   - Bilateral renal artery stenosis
   - CKD

Classification of heart failure 00:12:33

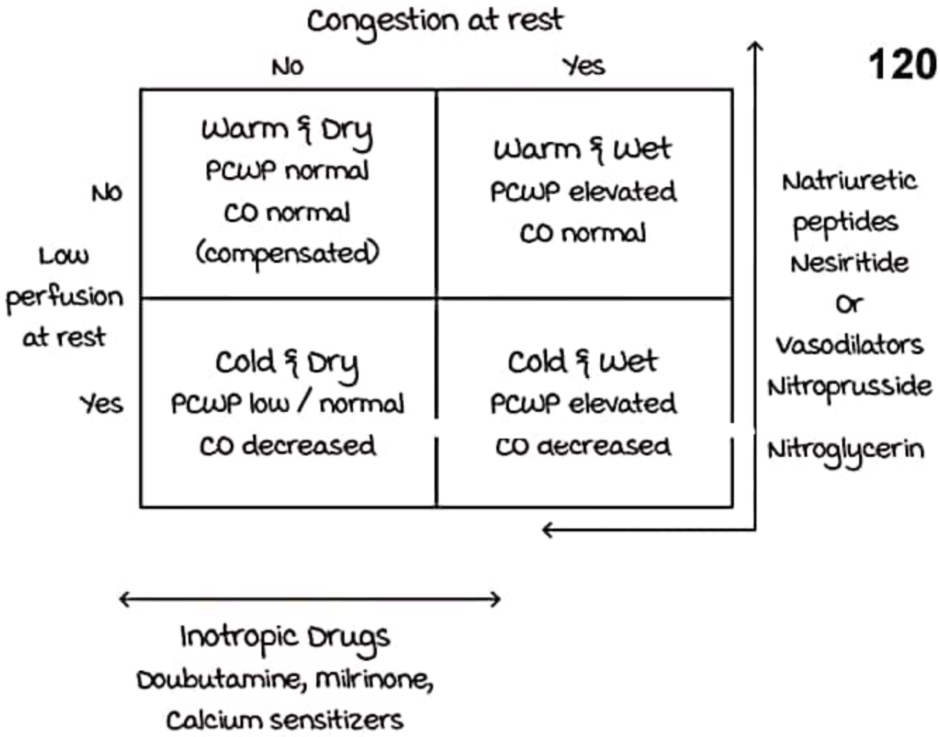


Clinical classification and treatment

Evidence for congestion
(elevated filling pressure)
orthopnea
High jugular venous pressure
increasing S_3
Loud P_2
Edema
Ascites
Rales (uncommon)
Abdominojugular reflux
Valsalva square wave

Evidence for low perfusion
Narrow pulses pressure
Pulsus altermans
Cool forearms and legs
may be sleepy, obtunded
ACE inhibitor-released
Symptomatic hypotension
declining serum sodium level
worsening renal function

Low perfusion at rest?	Congestion at rest? No	Congestion at rest? Yes
No	Warm and dry A	Warm and wet B
Yes	Cold and dry L	Cold and wet C



		Congestion at rest	
		No	Yes
Low perfusion at rest	No	Warm & Dry PCWP normal CO normal (compensated)	Warm & Wet PCWP elevated CO normal
	Yes	Cold & Dry PCWP low / normal CO decreased	Cold & Wet PCWP elevated CO decreased

Natriuretic peptides
Nesiritide
Or
Vasodilators
Nitroprusside
Nitroglycerin
Inotropic Drugs
Doubutamine, milrinone,
Calcium sensitizers

I. Warm and wet (most common)
  - Normal BP group Normal BP group with RV failure presents with peripheral overload
  - Hypertensive profile manifest with pulmonary edema
  - Features of elevated filling pressure are present features of low perfusion → cold extremities, narrow pulse pressure

II. Cold and wet (2nd most common)
  - Pulmonary edema + Cardiogenic shock
  - Features of low perfusion are present

III. Warm and dry (Rare)
  - PCWP – Normal; Cardiac output – Normal

IV. Cold and dry (Rare)
  - PCWP: Normal; Cardiac output – Decreased
  - LV systolic failure
  - Heart failure with reduced EF

BNP and NT-pro BNP 00:17:35

- In patients with intermediate probability of heart failure >900 pg/ml of NT- pro BNP is diagnostic
- It has more negative predictive value
- It can be falsely high in renal failure and low in obese

Treatment

00:18:42

- Non rebreather facemask delivering high flow O_2 if there is hypoxia
- Patient with pulmonary edema: Start I.V. Diuretics without delay [Furosemide (Lasix) ⇒ maximum of 360 mg (100mg → 100 mg → 100 mg → 60 mg)]
  [Torsemide ⇒ 100 mg in 500 ml normal saline over 40 minutes]

Vasodilator therapy

- Nitroglycerin as an adjunct to diuretic therapy in patients with pulmonary edema (3-6 mg i.v. bolus or 5μg /min infusion → 10 μg /min → 25 μg /min
- Early vasodilator therapy with nitroprusside in patients with HTN or acute AR / MR for urgent afterload reduction. Stop if symptomatic hypotension
- No routine recommendation for nesiritide therapy (Nesiritide is recombinant brain natriuretic peptide)

Warning : Not all points are covered in the notes, especially conceptual explanations. Please use the notes in conjunction with marrow Edition 4 videos.

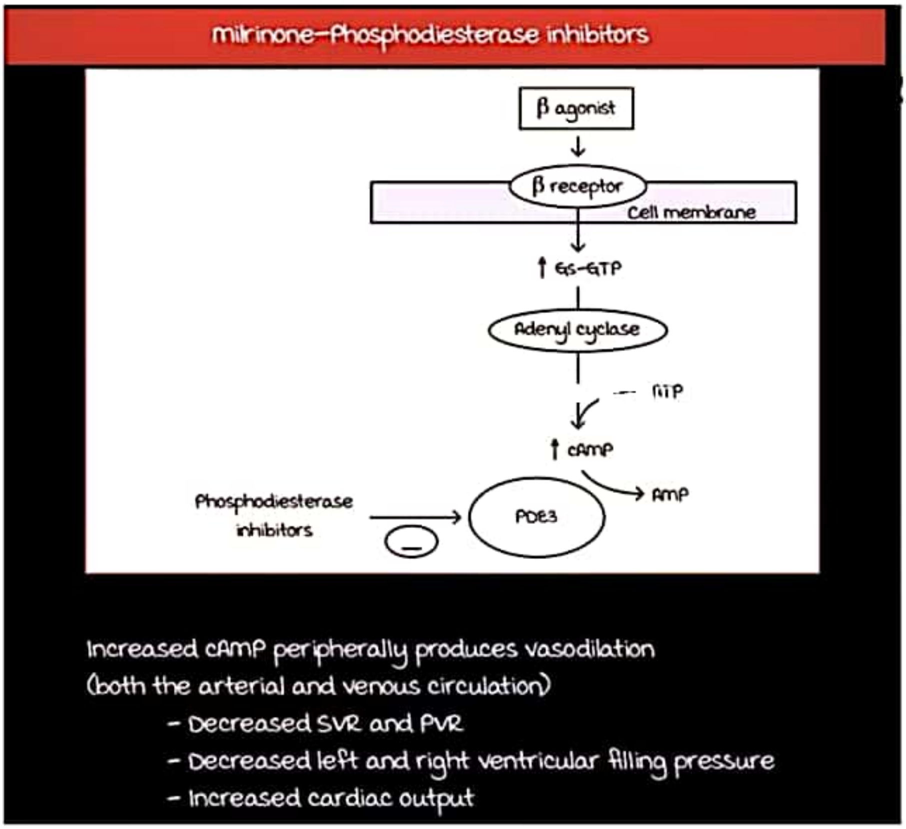
Ionotropes

- HF with reduced EF requires ionotropic therapy
- HF with preserved EF requires vasopressor support

⇒ Ionotropic therapy can be given with dopamine, dobutamine or milrinone. They temporarily maintain perfusion until IABP or ECMO

⇒ Levosimendan can also be tried

⇒ Vasopressor support in patient with HF with preserved EF is given with Noradrenaline or vasopressin

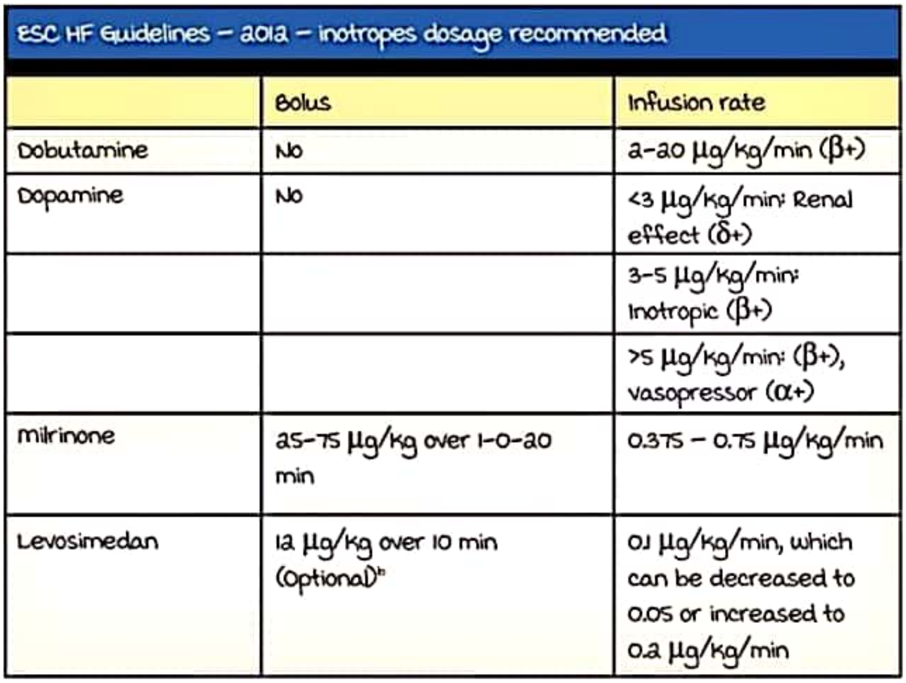


milrinone–Phosphodiesterase inhibitors

β agonist
β receptor
Cell membrane
↑ Gs-GTP
Adenyl cyclase
GTP
↑ cAMP
AMP
Phosphodiesterase inhibitors
PDE3
−

Increased cAMP peripherally produces vasodilation (both the arterial and venous circulation)

- Decreased SVR and PVR
- Decreased left and right ventricular filling pressure
- Increased cardiac output



ESC HF Guidelines – 2012 – inotropes dosage recommended

	Bolus	Infusion rate
Dobutamine	No	2–20 μg/kg/min (β+)
Dopamine	No	<3 μg/kg/min: Renal effect (δ+)
		3–5 μg/kg/min: Inotropic (β+)
		>5 μg/kg/min: (β+), vasopressor (α+)
Milrinone	25–75 μg/kg over 1-0-20 min	0.375 – 0.75 μg/kg/min
Levosimedan	12 μg/kg over 10 min (Optional)[b]	0.1 μg/kg/min, which can be decreased to 0.05 or increased to 0.2 μg/kg/min

Active space

CHRONIC HEART FAILURE

Definition of heart failure(HF) 00:00:23

Heart failure is a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood.

Types:

1. Acute heart failure
2. Chronic heart failure
    a) Heart failure with reduce EF (< 40% EF) or Systolic heart failure
    b) Heart failure with preserved EF (> 50% EF) or Diastolic heart failure

No much difference in systolic or diastolic dysfunction with respect to mortality

Causes of HFrEF or systolic heart failure 00:03:22

1. Ischemia (Ischemic Cardiomyopathy)
2. Dilated cardiomyopathy

Diastolic heart failure: Definition and causes 00:04:15

1.Definition :

European Society of cardiology (working group) defines diastolic heart failure as

1) Presence of signs or symptoms of congestive heart failure
2) Presence of normal or only mildly abnormal left ventricular systolic function
3) Evidence of abnormal LV relaxation, filling diastolic distensibility or diastolic stiffness.

Causes

1. Hypertension (Elderly females with hypertension are more prone)
2. Obesity

3. CKD
4. Diabetes mellitus + CKD
5. Coronary Artery Disease
6. Restrictive Cardiomyopathy
7. Hypertrophic Cardiomyopathy

Clinical features in heart failure 00:07:11

* Features due to decrease in Cardiac output: Fatigue, dyspnea on exertion, cachexia, weight loss, cold extremities

* Features due to elevated filling pressure (which can lead to volume overload): ↑ JVP, Edema, Ascites

* ↑ LV filling pressure can lead to pulmonary edema

	Systolic dysfunction	Diastolic Dysfunction
• Hypertension	++	+++
• Coronary Artery Disease	+++	+
• Third heart sound (S3)	+++	+
• Fourth heart sound (S4)	+	+++
• Rales	++	++
• JVP	++	+
• Displaced apex	++	−

Precipitants of pulmonary edema 00:11:28

The precipitants of pulmonary edema and the factors which can lead to decompensation are

- Anaemia
- Atrial Fibrillation
- myocardial ischemia
- Hypo & Hyperthyroidism
- Renal Insufficiency
- Discontinuation of medications

Heart Failure = LV dysfunction
↓
Increased LV end diastolic pressure
↓
Increased Pulmonary venous pressure (Pulmonary venous HTN)
↓
Pulmonary interstitial and alveolar edema

⇒ Pulmonary edema is generally seen more common in Systolic HF than in diastolic HF

⇒ In diastolic HF, right sided HF Symptoms are more

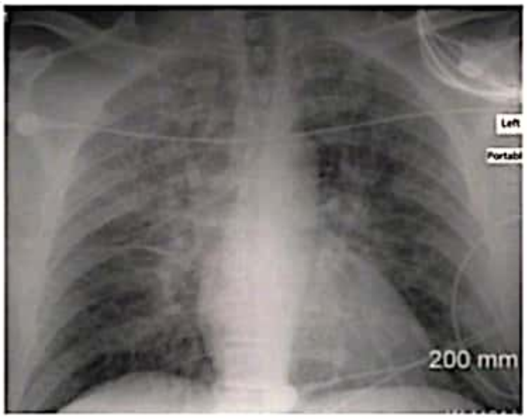
⇒ In LV Systolic HF, the end diastolic pressure increases such that pulmonary edema is easily developed

⇒ In RV Systolic failure, LA pressure is not increased as enough blood does not return to LA

⇒ Diastolic HF generally tends to involve right side > left side

⇒ Systolic HF generally tends to involve Left side > Right side

Compensatory mechanism to maintain cardiac output 00:15:34



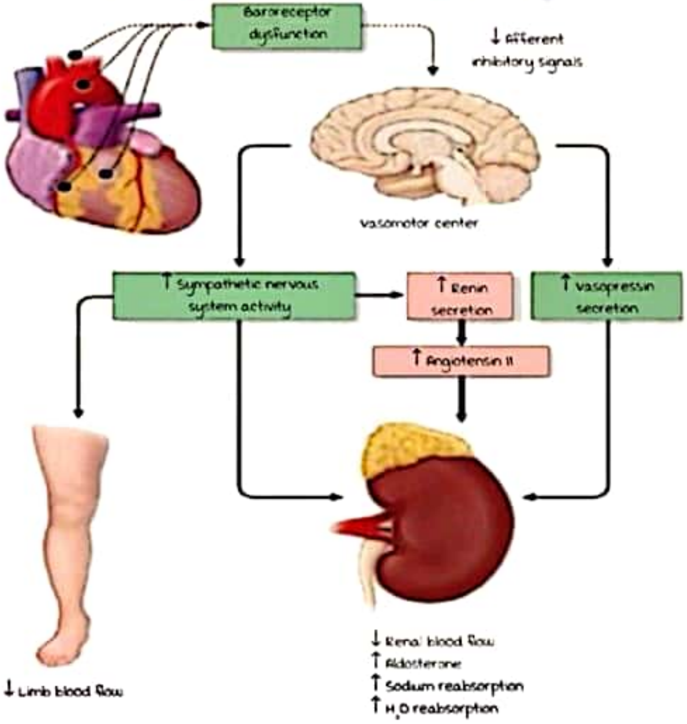
- Heart failure begins after an index event, produces an initial decline in the heart's pumping Capacity.
- After this initial decline in pumping capacity, a variety of compensatory mechanisms are activated, including the adrenergic nervous system, the renin – Angiotensin – aldosterone System and the cytokine System
- In the short term, these Systems are able to restore cardiovascular function to a normal homeostatic range with the result that the patient remains asymptomatic

- However, with time, the Sustained activation of these Systems can lead to Secondary end – organ damage within the ventricle with worsening left ventricular remodelling and Subsequent cardiac decompensation

Remodelling mechanism 00:17:13

- Activation of Sympathetic nervous system
- Activation of RAS
    - AT_1 – Vasoconstriction
    - AT_2 – Vasodilatation
- AVP
- ANP/BNP – Causes natriuresis, Vasodilatation
- Endothelin: ET(A) : Vasoconstriction

  ET(B) : Vasodilatation (NO, prostacyclin)


Baroreceptor dysfunction
↓ Afferent inhibitory signals
vasomotor center
↑ Sympathetic nervous system activity
↑ Renin secretion
↑ Vasopressin secretion
↑ Angiotensin II
↓ Limb blood flow
↓ Renal blood flow
↑ Aldosterone
↑ Sodium reabsorption
↑ H₂O reabsorption

Framingham criteria 00:18:10

It includes the following

* PND – Sign of impending LV failure with normal RV

*JVP – Sign of RV failure

* Crepitations – Sign of LV failure

* Cardiomegaly – Sign of LV failure

* S_3 (Third heart Sound) – Seen in Left heart failure

* Acute pulmonary edema – Seen in left heart failure

* Hepato – jugular reflex – seen in impending right heart failure

Note: It does not include hepatomegaly

Investigation 00:19:29

1. ECG – LVH, old evidence of ACS
2. ECHO – Can assess systolic and diastolic function
3. cardiac MRI – Gold standard to diagnose heart failure

Management 00:20:01

I. HF with preserved EF: underlying cause should be treated first

II. HF with reduced EF: Drug can be divided into 2 groups

Drugs with symptomatic benefit

I) Ionotropes
II) Diuretics
III) Vasodilators

Drugs with mortality benefit

I) Beta-blocker
II) ACE I / ARB / ARNI
III) Aldosterone antagonist
IV) Hydralazine + Nitrate

Diuretics

- maintain volume (weight loss of 1 kg/day)
- Congestive symptoms are best treated with diuretics
- They slowdown the ventricular remodelling
- Reduce LV filling pressure

⇒ Loop diuretics are drug of choice

⇒ They increase free water clearance

- Furosemide 40 mg
- Torsemide 20 mg (longer t½ and ↑ bioavailability)

Note:

- In patient with low cardiac output(hypotension) Diuretics can further decompensate
- Braking phenomenon – It means if one part of the tubule is blocked then the other part becomes extremely responsive and take up more salt and water, which can lead to diuretic resistance

⇒ Thiazide diuretics to be added in case of diuretic resistance

⇒ Only thiazide diuretic recommended in renal failure is metolazone

⇒ Cardiorenal syndrome ↓ cardiac output ⟶ ↓ Renal perfusion
↓
Renal failure

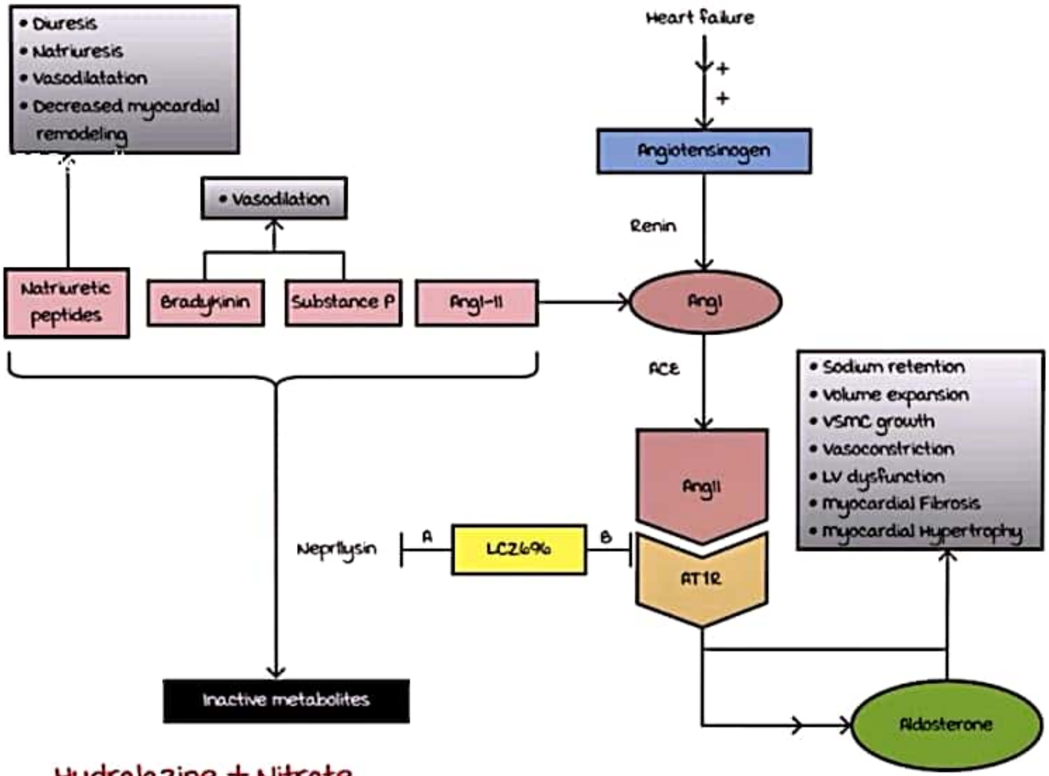
ARNI

⇒ Angiotensin receptor blocker + Neprilysin inhibitor
↓ Valsartan (26 mg) ↓ sacubitril (24 mg)

⇒ ARNI is better than ACE/ARB

⇒ Initial treatment plan is to use diuretics (furosemide) + ARNI

LCZ696 – sacubitril / valsartan – Entresto


• Diuresis
• Natriuresis
• Vasodilatation
• Decreased myocardial remodeling
Heart failure
+
+
Angiotensinogen
• Vasodilation
Renin
Natriuretic peptides
Bradykinin
Substance P
AngI-II
AngI
ACE
• Sodium retention
• Volume expansion
• VSMC growth
• Vasoconstriction
• LV dysfunction
• myocardial Fibrosis
• myocardial Hypertrophy
AngII
Neprilysin
A
LCZ696
B
AT1R
Inactive metabolites
Aldosterone

Hydralazine + Nitrate

⇒ It is used in patients intoletrant to diuretics + ARNI/ACEI

ACE inhibitors

⇒ First line in treatment of symptomatic LV dysfunction

⇒ ACE inhibitor can cause – First dose hypotension
Renal failure
Hyperkalemia

Beta blockers

⇒ Once volume control is achieved with diuretics + ARNI/ACEI, β – blockers is added

⇒ It prevents LV remodelling

⇒ Symptomatic or asymptomatic with 40% EF start beta blocker

⇒ Start at the lowest dose

⇒ Worsening of fluid retention can occur after 3–5 days (Hence volume control has to be achieved before starting beta – blocker)

⇒ Contraindicated in acute decompensated heart failure

⇒ Beta blockers approved in heart failure are
  - metoprolol : 25 mg OD
  - Bisoprolol : 1.25 mg OD
  - Carvedilol : 3.125 mg BD

Beta blockers in heart failure

* Patient with LV Systolic dysfunction – beta blockers reduced mortality and rehospitalization rates

* Patient with preserved Systolic function – beta blocker therapy was associated with improvement in mortality or rehospitalization

Beta blocker in diastolic heart failure

- Control the heart rate
- Maximize the diastolic filling period
- Reduce blood pressure
- Reduce myocardial ischemia
- Promote regression of left ventricular hypertrophy

Aldosterone antagonist

If LV ejection fraction <40% while on diuretic + beta blocker + ARNI and there is no hyperkalemia and no renal failure, then there is definite mortality benefit on starting with spironolactone or eplerenone

Ivabradine

- Inhibitor of the I_f Current in the SA node
- Second line before considering digoxin (No role of digoxin)
- Use when HR > 70 beats/ min
- Causes bradycardia

Note:

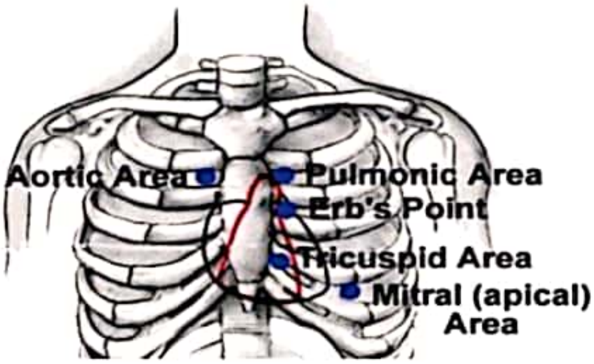
- A combination of ARNI + diuretic should be the initial treatment in most patients with the early addition of beta blocker
- Ivabradine for stable patients with HR > 70 beats/ min on maximally tolerated beta blocker use
- Resistant heart failure with normal QRS – Implantable cardio-verter defibrillator (ICD)
- EF < 35% with LBBB or QRS > 120mg – Cardiac Resynchronization Therapy (CRT)

MURMURS

Areas of auscultation

00:01:10

Areas of auscultation



- Aortic area: 2nd right ICS
- Erb's area (Neo aortic): 3rd left ICS adjacent to the sternum
- Pulmonary area: 2nd left ICS
- Tricuspid area: 4th and 5th ICS adjacent to the left sternal border
- Mitral area: At the cardiac apex
- Axillae: For radiation of Pansystoic murmur of MR
- Back: Interscapular area- Murmurs of coarctation of aorta
  Infrascapular area- Bruit of collateral circulation
- Carotids: Conduction of systolic murmurs of aortic valve disease
- Above and below the clavicles: Continuous murmur of PDA
- Femoral artery: Duroziez's murmur of AR

Position of the patient

00:03:24

1. For mitral area – Left lateral decubitus
2. For tricuspid area – Supine
3. For basal area – Sitting and leaning forward

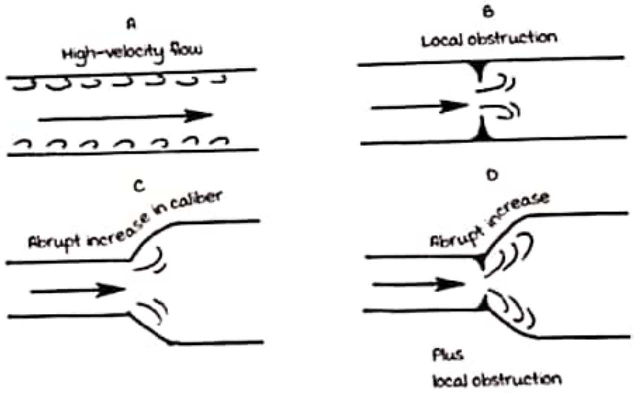
Definition and mechanism

00:03:50

A cardiac murmur is defined as relatively prolonged series of auditory vibrations of varying intensity (loudness), frequency (pitch), timing, quality, configuration and duration mechanism

Turbulence is the prime factor responsible for murmurs

1. High flow through orifices
2. Forward flow through irregular or narrow orifice or into dilated vessel
3. Regurgitant flow through an incompetent valve or septal defect or PDA


A
High-velocity flow
B
Local obstruction
C
Abrupt increase in caliber
D
Abrupt increase
Plus
local obstruction

Evaluation of heart murmurs

00:04:29

- Timing
- Duration
- Location
- Intensity or loudness (grace of murmur)
- Frequency or pitch
- Bell or diaphragm
- Radiation
- Pharmacological aids and physical maneuvers

Note:

- Almost all murmurs are high pitched
- Pure low-pitched murmurs are
  - Austin flint murmur (mid Diastolic murmur[MDM])
  - murmur of MS (MDM)
- Low pitch murmur have thrill and auscultated with bell of the stethoscope
- murmur of AS (both high & low pitch component present)
- murmur of HCM is medium pitched
- Systolic murmur: Intensity is important
- Diastolic murmur: Duration is important

Active space

Grades of murmur

00:06:02

Grade 1 ⇒ Faintest murmur that can be heard under optimal conditions. Very soft, heard with difficulty, murmurs that only cardiologists hear

Grade 2 ⇒ Soft, readily audible

Grade 3 ⇒ Prominent murmur

Grade 4 ⇒ Loud murmur that is palpable

Grade 5 ⇒ Loud heard with part of stethoscope on chest wall

Grade 6 ⇒ Loud enough to be heard with stethoscope just removed from contact with the cheat wall

Note:

- High pitch murmurs are soft, blowing murmur
- Low pitch murmurs are harsh, rough murmur

Loudness of murmur

00:07:07

[redacted]	Factors affecting the loudness of heart murmurs
Increased intensity	High cardiac output (hyperdynamic states) Thin chest wall Narrow thoracic diameter; for example, straight back, pectus excavatum Anemia (decreased blood viscosity) Tortuous aorta (close to chest wall)
Decreased intensity	Obesity Muscular or thick chest wall Obstructive lung disease Barrel chest (increased anteroposterior diameter) Pericardial thickening or fluid Decreased cardiac output (congestive heart failure, low ejection fraction)

Systolic murmurs

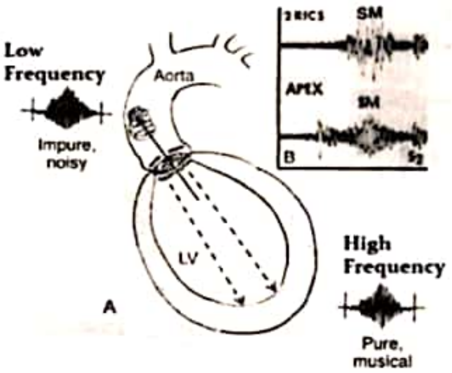
Ejection systolic murmur (ESM)

- Starts after S_1 and ends with S_2
- Innocent ESM
  - most often associated with anaemia
  - mid systolic peaking
  - Grade is ≤ 3/6
  - innocent murmur
- Cause of ESM
  - AS
  - PS
  - HCM
  - Aortic sclerosis

Murmur of AS

1. High pitch → low pitch murmur
2. ESM
3. 2nd right ICS
4. Diaphragm of stethoscope
5. Sitting and leaning forward position in full expiration
6. No change with any maneuvers
7. Decrease with valsalva and standing
   (Note: Only murmur to increase with valsalva and standing are HCM and MVP)
8. Gallavardin's Phenomenon
   - Described by Louis Gallavardin in 1925
   - High frequency component: Radiates to apex (soft, musical)
   - Low frequency component: Radiates to neck (harsh, noisy)

Gallavardin dissociation



- Described by Louis Gallavardin in 1925

9. Longer the duration of murmur and later the peaking in systole more severe is AS provided Cardiac Output(CO) is within limits

10. High CO lesions can overestimate severity of AS and low CO can underestimate the severity

11. AS murmur best heard at LLSB without conduction is diagnostic of subvalvular AS

12. Carotid murmur without 2nd right ICS murmur is diagnostic of supravalvular AS

13. AS murmur audible only at apex is calcific AS with COPD

Murmur of HCM

1. No radiation to carotid
2. ↑ on valsalva and standing

Murmur of MVP

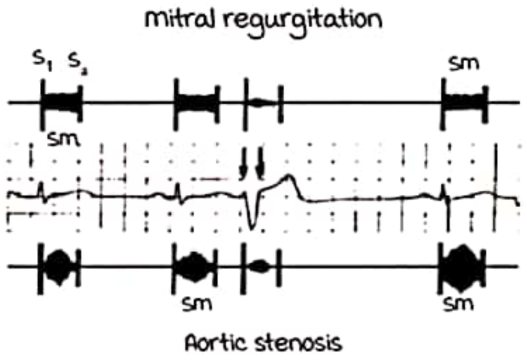
- With standing, venous return decrease, the heart becomes smaller and prolapse occur earlier. The click and murmur is more closer to S_1
- With squatting, venous return increase, causing an increase in left ventricular chamber size. The click and murmur occur later and move away from S_1

Differentiation of AS from MR murmur

Soft blowing murmur at apex

MR
- Radiates to back

AS (due to gallavardin phenomenon)
- No radiation to back
- Post ectopic increase in intensity



ESM of aortic sclerosis

- Short murmur
- Early peaking
- more high pitched
- S_2 may be more accentuated as there is no much calcification

ESM of PS

- Best heard at pulmonary area radiating to supraclavicular area
- S_4
- Giant 'a' wave
- Wide split S_2
- Longer duration and later peaking have more severity (This rule is satisfied in all except TOF)

ESM of severe AR

- No precordial thrill
- Shorter murmur
- Early peaking

Pansystolic murmurs

00:20:36

- Present in entire duration Of systole
- Seen in
  - MR
  - TR
  - VSD

PSM of MR

1. High pitched
2. Left lateral position
3. At apex
4. Soft blowing
5. Best heard with diaphragm of stethoscope
6. Soft blowing radiation to axilla
7. Best heard during end expiration

Note:

⇒ Early systolic murmur in MR is seen in Acute MR

⇒ Systolic thrills are less common in high frequency murmur and if present suggests infective endocarditis or chordae rupture

⇒ Does not increase with expiration

⇒ Jet directed to left and posteriorly

⇒ Cardiomegaly +

⇒ S_3

⇒ Loud S_1

PSM of TR

- High pitched
- Left lower sternal border
- Heard with diaphragm of stethoscope
- Soft blowing
- No conduction of murmur
- Best heard in inspiration

Carvallo's sign

- The intensity of TR murmur increase with inspiration
- This is due to increase in RV volume with inspiration which is converted into ↑ stroke volume
- When RV fails, Carvallos sign disappears

PSM of VSD

- MC site heard as lower left sternal border
- Can be heard anywhere from pulmonary area to tricuspid area
- Thrill is common
- No conduction
- Rough murmur (combination of both frequency)
- Fails to increase with inspiration
- Biventriclular enlargement

Differential diagnosis of a pansystolic murmur

Feature	MR	TR	VSD
Site of best audibility	Apex	Tricuspid area	LSB, anywhere from pulmonary to tricuspid area
Grade	Thrill rare	Thrill does not occur	Thrill is common
Selective conduction	Axilla and back	On selective	No selective conduction
Character	Soft, blowing high frequency	Soft blowing high frequency	Rough, harsh, combination of high and low frequencies
Relation to physiological act	Fails to increase during inspiration	Increase during inspiration	Fails to increase during inspiration
Accompanying failure	LV enlargement diminished S_1, LV S_3 apical diastolic murmur	Signs of PAH RV enlargement elevated JVP with prominent v wave	Biventricular enlargement signs of PAH, apical diastolic murmur

Diastolic murmurs

00:26:12

- Always signify abnormal structural or functional cardiovascular system
- Graded by duration rather than intensity
- Thrill +

MDM of MS

- Low pitched, mid-diastolic murmur with pre-systolic accentuation
- Rough rumbling
- Left lateral
- Bell of stethoscope
- No radiation
- Expiration
- Severity of MS is inversely related to S_2-OS interval

Austin Flint murmur

mechanism:

1. ↑ Filling pressure in diastole
2. Vibration of MV leaflets due to AR jet impinging on it
3. Deformity and shuddering of MV apparatus by regurgitant jet
4. Turbulent flow of the reguritant jet colliding with incoming blood from the left atrium

MS vs Austin Flint murmur

	MS	Austin Flint
Rhythm	AF	Normal
Signs of wide pulse pressure	Absent	Present
Cardiomegaly and LV heave	Absent	Present
RV lift	Present	Absent
S_1	Loud	Normal to decreased
Opening snap	Present	Absent
S_3	Absent	Present
Diastolic thrill	Present	Absent

Carey coomb murmur

- Seen in acute rheumatic fever
- mid-diastolic

Murmur of tricuspid stenosis (TS)

- mid diastolic murmur
- Murmur increase with inspiration
- No pulmonary hypertension
- 'a' wave in JVP

Note:

⇒ MDM in MR ⇒ Flow MDM, no pre-systolic accentuation
⇒ S_3^+
⇒ soft S_1

Early Diastolic murmur- AR, PR

1. Murmur of AR
- High frequency
- End expiration
- Sitting and leaning forward
- Neo aortic area
- Thrill rare
- Diaphragm of stethoscope
- Right sternal border suggests root disease
- Murmur becomes short in acute AR or LVF
- Increase with isometric intensity (hand grip)
- ↓ HR, there is increase intensity

2. Murmur of PR
- Graham steel murmur
- PAH +

Warning - Not all points are covered in the notes, especially conceptual explanations. Please use the notes in conjunction with Marrow Edition 4 videos.

Murmur with eponyms 00:33:16

Murmur with eponyms

Austin Flint murmur	Mid-diastolic rumbling sound present in aortic regurgitation
Gibson's murmur	Continuous murmur of PDA
Roger's murmur	Holosystolic murmur of VSD
Graham steel murmur	Soft, blowing, decreasendo diastolic hypertensive PR murmur
Still's murmur	Benign vibratory ejection systolic murmur in children
Rytand's murmur	Short crescendo decrescendo diastolic murmur in CHB

Carey coombs murmur	Short mid diastolic murmur seen in acute rheumatic mitral valvulities
Dock's murmur	Diastolic murmur with presystolic peak, seen in proximal LAD stenosis
Cabot – locke murmur	Diastolic murmur at the left sternal border, seen in severe anemia
Key-hodgkin murmur	Diastolic murmur of aortic regurgitation; with retroversion of the aortic valve leaflets
Cole cecil murmur	EDM of AR, best heard at apex, or in mid axillary line rather than at sternal border

Continuous murmurs 00:35:39

- A continuous murmur is one that begins in systole and extends through S_2 into part or whole of diastole
- It bridges systole and diastolic, extending past the S2 without any change in character
- Need not occupy the entire cardiac cycle. Presence of murmur throughout both phases of the cardiac cycle is not necessary

Prerequisite

- murmur should overlap S_2 and spill over to diastole with no respect to boundaries of cardiac cycle
- No change in character of murmur from systole to diastole
- Differs from a to and fro murmur (Eg. AS + AR) and systolic – diastolic murmur (Eg. VAD + AR)

To and Fro murmur (Biphasic murmur)

- Occuring through a single channel
- Occupies mid systole and early diastole
- Does not peak around S2
- Eg. AS with AR

Continuous murmur	To and Fro murmur
1. Unidirectional	Bidirectional
2. S_2 engulfed by murmur	S_2 heard well

Systolico- diastolic murmur

- Occurs in systole and diastole channel
- occurs through different channels
- Does not peak around S2
- Causes – VSD with AR

Features	PDA	VSD with AR
Heart murmur	Continuous	Systolico diastolic
Site	1st & 2nd LICS	4th LICS
S2	Engulfed by the murmur	Well heard
Eddy sounds	Eddy sounds	Absent

Classification of continuous murmur

Myers classification:

Physiological classification of continuous murmur.

1) Caused by rapid flow

2) Caused by high to low pressure shunts

3) Secondary to localized arterial occlusion

I. Contiuous murmurs caused by rapid blood flow

- Venous hum
- Mammary souffle
- Hemangioma
- Hyperthyroidism
- Acute alcoholic hepatitis – arterial bruit
- Neoplasms like hepatoma, RCC
- Paget's disease

II. Continuous murmurs caused by high to low pressure shunts

1. Systemic artery to pulmonary artery
    - PDA
    - AP window
    - Truncus arteriosus
    - Pulmonary atresia
    - Anomalous left coronary artery from the pulmonary artery

2. Systemic artery to right heart:
    - Ruptured sinus of valsalva
    - Coronary AV fistula

3. Left to right atrial shunting:
    - Lutembacher syndrome (mitral atresia + ASD)

4. Venovenous shunts
    - Anomalous pulmonary veins
    - Porto-systemic shunts

5. Arteriovenous fistula:
    - Systemic or pulmonary

III. Secondary to localized arterial obstruction

- Coarctation of aorta
- Branch pulmonary stenosis
- Carotid occlusion
- Celiac mesenteric occlusion
- Renal occlusion
- Femoral occlusion
- Coronary occlusion

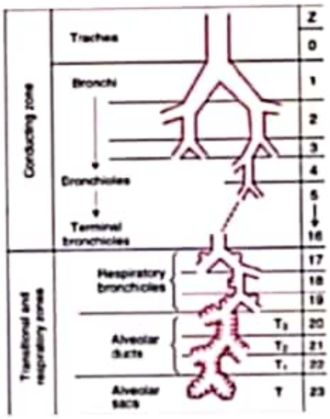
INTRODUCTION TO PULMONOLOGY

Weibel's airway generation

00:13:26

- Total – 23 airway generations
- Conducting zone – 1 – 16
  - Bronchi upto terminal Bronchiole
  - Trachea – Generation zero
- Respiratory zone – last 7
  - Respiratory Bronchiole
  - Alveolar duct
  - Alveoli

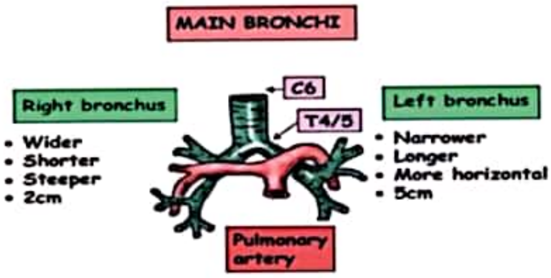
} Acinus


Conducting zone
Transitional and respiratory zones
Trachea
Bronchi
Bronchioles
Terminal bronchioles
Respiratory bronchioles
Alveolar ducts
Alveolar sacs
Z
0
1
2
3
4
5
16
17
18
19
T_3 20
T_2 21
T_1 22
T 23

- Respiratory bronchiole is also called Transitional zone → Generation 17, 18, 19
- Air present in the conducting airways is called anatomical dead space and is 150 ml

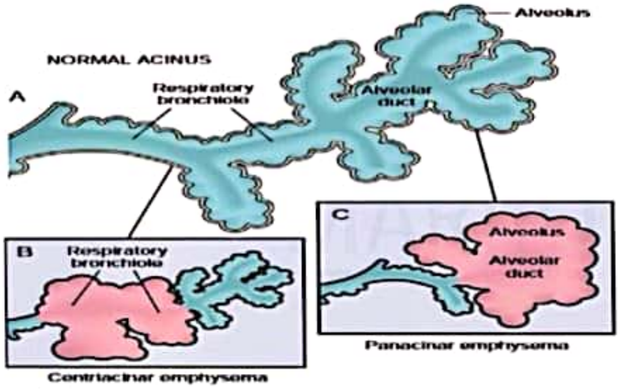
↓

No role in respiration


MAIN BRONCHI
Right bronchus
• Wider
• Shorter
• Steeper
• 2cm
C6
T4/5
Left bronchus
• Narrower
• Longer
• More horizontal
• 5cm
Pulmonary artery

Inhaled foreign body is much more likely to enter the right bronchus because of the above facts

- Rt. Bronchus is more in-line with the trachea
- Basic functional unit of lung → acinus
- 3 terminal Bronchioles with their acini → Lobule → Lobes
- Centri acinar Emphysema : Respiratory bronchiole is involved
- Pan acinar Emphysema : Alveolar duct + Alveolus are involved

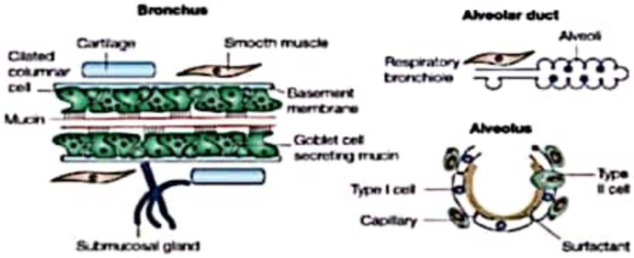

NORMAL ACINUS
A
Respiratory bronchiole
Alveolar duct
Alveolus
B
Respiratory bronchiole
Centriacinar emphysema
C
Alveolus
Alveolar duct
Panacinar emphysema

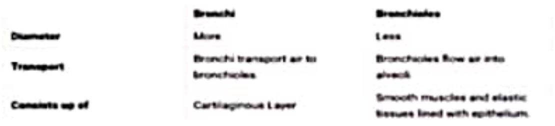
Active space

Functional points

00:13:26

- Cartilage + Submucosal glands → Only in trachea, Bronchi
- Cilia → upto Respiratory bronchiole
- Smooth muscles → maximum in terminal Bronchiole .
- Pseudo stratified ciliated columnar epithelium → seen in all the Respiratory tract
- Cilia is seen only upto respiratory bronchiole after which it is Non ciliated cuboidal epithelium.
- Vocal cords → Stratified Squamous Epithelium

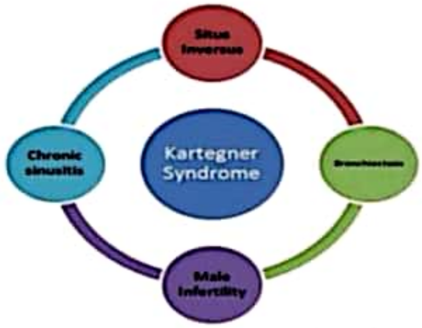

Bronchus
Cartilage
Smooth muscle
Ciliated columnar cell
Basement membrane
Mucin
Goblet cell secreting mucin
Submucosal gland
Alveolar duct
Alveoli
Respiratory bronchiole
Alveolus
Type I cell
Type II cell
Capillary
Surfactant

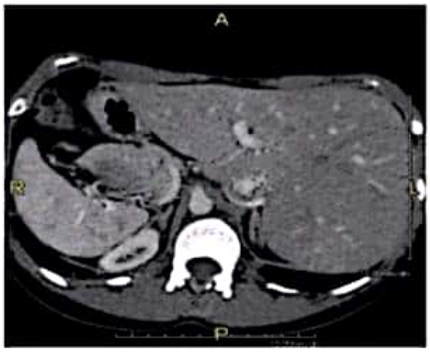


	Bronchi	Bronchioles
Diameter	More	Less
Transport	Bronchi transport air to bronchioles	Bronchioles flow air into alveoli
Consists up of	Cartilaginous Layer	Smooth muscles and elastic tissues lined with epithelium.

- Alveolar / Respiratory zone – final 7 generations
- Cilia beats towards the nasopharynx – called as mucociliary escalator mechanism.

Primary ciliary dyskinesia


Situs inversus
Kartegner Syndrome
Chronic sinusitis
Bronchiectasis
Male Infertility



- Also known as Kartagener's syndrome
- A.R – mode of inheritance
- median age of presentation – 5 years

Clinical features:

    - Recurrent otitis media
    - Sinus disease
    - Neonatal respiratory distress of unknown cause
- Pathology : Defective dynein arm

Active space

Gold standard investigation : measuring nasal nitric oxide levels → ↓ ↓

Cystic Fibrosis

- Mode of inheritance : A.R
- Defective gene : CFTR gene On Chromosome 7p
  ↓
  Cl^- ion defect
- Mutation : F508
- Pathology :
  Cilia – Normal, but the secretions are thickened in Bronchi, Biliary tract, intestine, reproductive system.
- Treatment : Ivacaftor – Cl^- Channel opener.

Cells in conducting airways :

1. Basal cells – Stem cells / progenitor cells.
2. Goblet cells – Secrete mucus
3. Clara / Club cells – Non – ciliated cuboidal epithelial cells in terminal bronchiole, involved in 1) Detoxification of Xenobiotics
   2) Progenitor for bronchiolar cells.
4. Kulchitzky cells – Neuroendocrine cells characterised by dense core vesicles which contain serotonin, calcitonin, CGRP

- Most potent Bronchoconstrictor → leukotrienes > Substance P
  - Maximum Bronchoconstriction – 6 A.m
- Potent Bronchodilator → VIP (Vasoactive Intestinal Peptide) Or NANC (Non adrenergic non cholinergic peptide)
  - Maximum physiological Bronchodilation – 6 P.m
- Test used to assess airway hyper-responsiveness → Methacholine Challenge test.

Cells of Respiratory System :

00:29:00

Cells of respiratory system

Type I pneumocyte
↓
- 90 – 95%
- Flat, Non dividing Cells
- More prone for

Type II pneumocyte
↓
5%
- Also Known as Granular pneumocyte / Stem cells
- Rounded cells

Pulmonary alveolar macrophages

↓

- Typically with Bleomycin, amiodarone
- Damage to type I Cells

↓

- Hyperplasia of II Cells

- Functions :
  - Surfactant Production
  - Stem cells

Stem cells in respiratory system :

1. Basal stem cells in the conducting zone.
2. Clara cells / club cells – Progenitors for bronchiolar cells
3. Type II Pneumocyte – progenitors for alveolar cells

Surfactant

00:32:46

- Reduces surface tension → prevents collapse of Lung
- Composed of lipoprotein.

↓

Predominantly Lipid

Dipalmitoyl phosphatidyl choline(Lecithin) > Sphingomyelin

- Fetal lung maturity : L/S ratio
- Surfactant proteins ;
  - Sp A, D → Role in innate immunity
  - SP A, B, C, D
- Surfactant is stored in Lamellar bodies inside type 2 pneumocytes.

Functions :

Decrease the surface tension

↓

Prevents collapse of lung

↓

Increase the compliance and prevents pulmonary edema.

- Excess surfactant is cleared by GM – CSF
- Antibody against GM – CSF → Pulmonary alveolar proteinosis (PAP)
- Drug used in Hyaline membrane disease → Beractant (Artificial Surfactant)
- Hormones that increase surfactant production → steroids, thyroxine.
- Hormone that decrease the production of surfactant → Insulin

markers of alveolar Cells ;

Alveolar cells markers

Type I cells
- Aquaporin 5
- Caveolin I
- Carboxy peptidase m

Type 2 cells
- SP – A
- SP – B
- Sp – C
- SP – D

Changes from trachea to alveoli

00:38:22

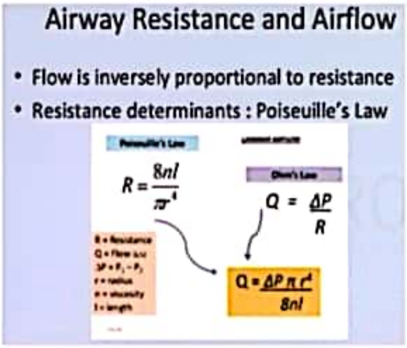
- Diameter
- Velocity
- Turbulence

} Decreases

- Total cross sectional area
- Resistance in Individual airways

} Increases, But resistance decreases In Smaller airways.

- Flow rate = $\frac{p1 - p2}{R} = \frac{\Delta P}{R}$ (pressure difference) (resistance)



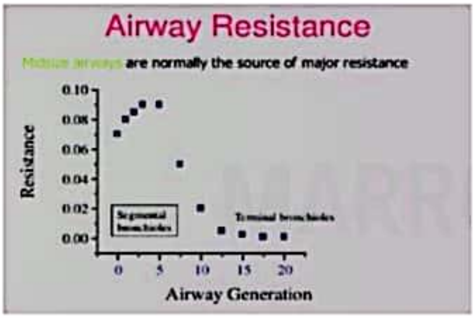
Airway Resistance and Airflow

- Flow is inversely proportional to resistance
- Resistance determinants : Poiseuille's Law

$R = \frac{8\eta l}{\pi r^4}$

$Q = \frac{\Delta P}{R}$

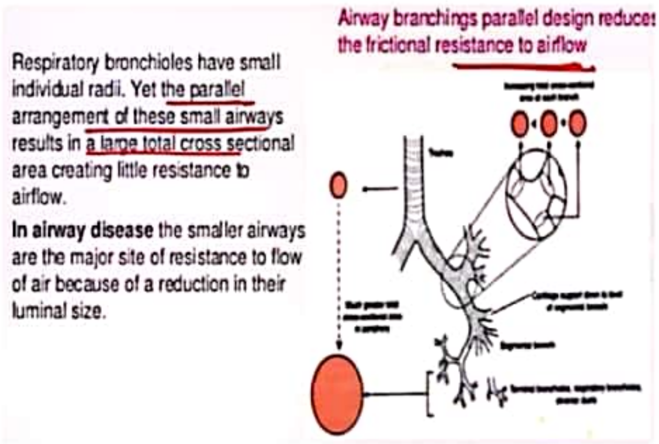
$Q = \frac{\Delta P \pi r^4}{8\eta l}$



Airway Resistance

Medium airways are normally the source of major resistance

- Flow rate ∝ 1/R = Ohm's law.



Airway branchings parallel design reduces the frictional resistance to airflow

Respiratory bronchioles have small individual radii. Yet the parallel arrangement of these small airways results in a large total cross sectional area creating little resistance to airflow.

In airway disease the smaller airways are the major site of resistance to flow of air because of a reduction in their luminal size.

- $R = \frac{8\,nl}{\pi r 4}$

- Maximum resistance → medium sized Bronchi (Not smaller airways like alveoli)

↓

It is because of the parallel arrangement of smaller airways.

↓

total cross sectional area ↑

↓

↓ The resistance to air in the smaller airways.

Reynold's number :

- Index to determine whether flow is laminar or turbulent.

$Re = 2\,rvd/\eta$ [r = Radius, v = Velocity, d = density η = viscosity]

- < 2000 – laminar – terminal bronchiole
- > 4000 – turbulent – at level of trachea
- 2000 – 4000 – transitional flow – all over the lungs

Pressures in respiratory physiology 00:00:37

Intra-pleural pressure

- At rest is negative

- Due to the vacuum space between lung & chest wall
- Due to presence of pleural lymphatics

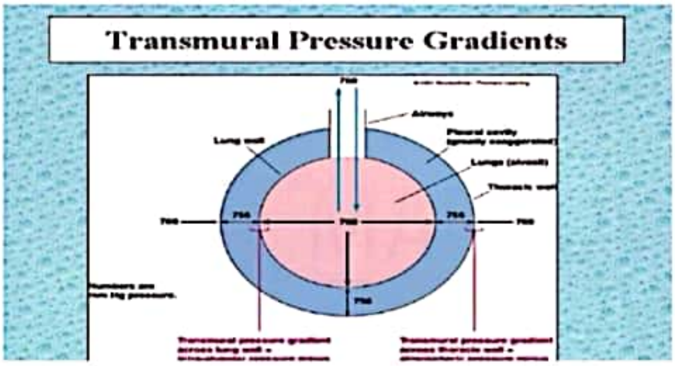
Intra-pulmonary pressure (alveolar)

- At rest is zero

Trans-pulmonary pressure

- intrapulmonary pressure − intrapleural pressure

Transmural (transpulmonary) pressure gradients :


Transmural Pressure Gradients
760
Airways
Lung wall
Pleural cavity (greatly exaggerated)
Lungs (alveoli)
Thoracic wall
760
756
760
756
760
756

- Gradient across lung (transpulmonary pressure)
  = Intrapulmonary pressure − intrapleural pressure
  → Intrapleural pressure at rest = −2 to −3 mmHg or −5 cm H_2O
  → 0 − (−5) = +5 cm of H_2O

- Gradient across chest wall
  = Intra atmospheric pressure − Intrapleural pressure
  = 0 − (−5)
  = +5 cm of H_2O

Linkage of lungs to thorax

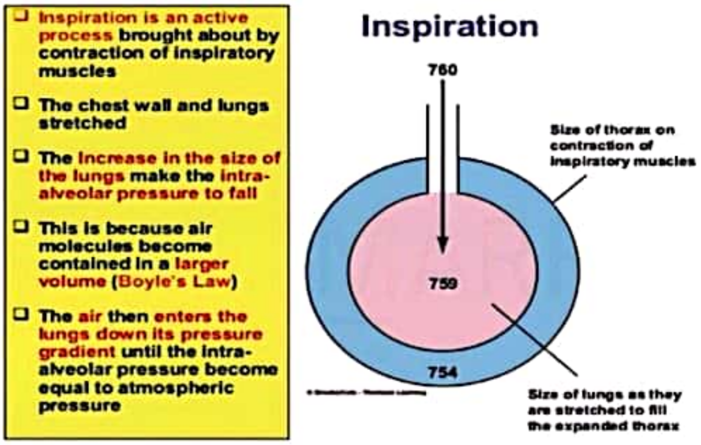
1. Intrapleural fluid cohesiveness
   → Pleural membranes [redacted]

2. Negative intrapleural pressure
   → helps to establish transpulmonary gradient

Inspiration and expiration

00:08:00

Inspiration

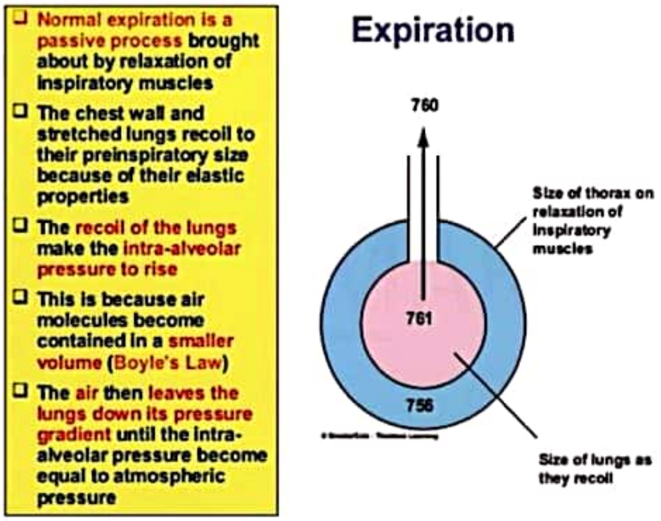


- ☐ Inspiration is an active process brought about by contraction of inspiratory muscles
- ☐ The chest wall and lungs stretched
- ☐ The increase in the size of the lungs make the intra-alveolar pressure to fall
- ☐ This is because air molecules become contained in a larger volume (Boyle's Law)
- ☐ The air then enters the lungs down its pressure gradient until the intra-alveolar pressure become equal to atmospheric pressure

Inspiration
760
Size of thorax on contraction of inspiratory muscles
759
754
Size of lungs as they are stretched to fill the expanded thorax

- Boyle's Law : $v \propto 1/p$ (V=volume, P = pressure)
- Intrapulmonary pressure falls : 0 to −1
- Once lungs are filled, gradient is lost it goes back to zero
- Throughout inspiration, intrapleural pressure becomes more negative
- Intrapleural pressure at end of inspiration = −6 to −7 mmHg
  or
  −12 cm of H_2O

Expiration



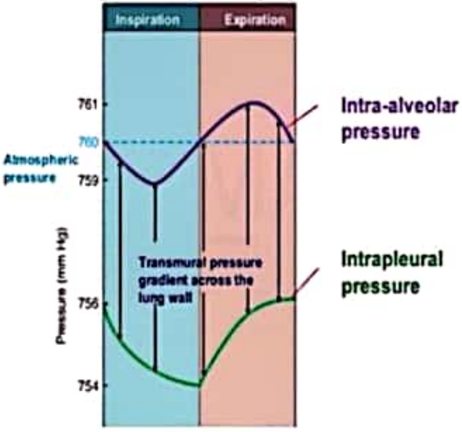
- ☐ Normal expiration is a passive process brought about by relaxation of inspiratory muscles
- ☐ The chest wall and stretched lungs recoil to their preinspiratory size because of their elastic properties
- ☐ The recoil of the lungs make the intra-alveolar pressure to rise
- ☐ This is because air molecules become contained in a smaller volume (Boyle's Law)
- ☐ The air then leaves the lungs down its pressure gradient until the intra-alveolar pressure become equal to atmospheric pressure

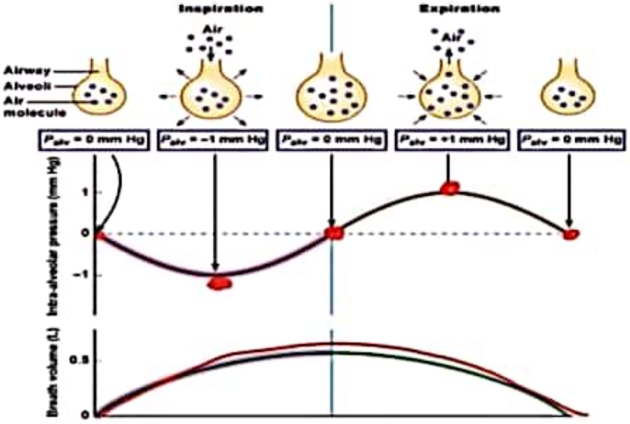
Expiration
760
Size of thorax on relaxation of inspiratory muscles
761
756
Size of lungs as they recoil

- Intrapulmonary pressure increases : 0 to −1 to 0 to +1 to 0

- Intrapleural pressure :
  - → Becomes positive
  - → moves to base pressure -2 to -3

Changes in intra-alveolar and intra-pleural pressures during the respiratory cycle





Transpulmonary pressure

00:13:47

- Transpulmonary pressure : = intra alveolar pressure − intrapleural pressure
  - → Distending pressure (pressure against which lung should be inflated)

- Factors opposing distension of lung :
  - → Surface tension
  - → Elastic forces in lung : loss of elastic attachment
    ↓
    Elastic recoil pressure falls
    ↓
    makes it easy to inflate the lung

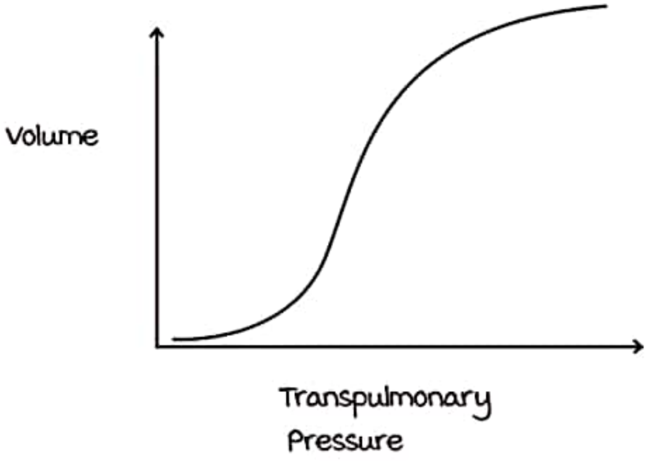
Active space

- ↑ in attachments : ↑ in fibrous tissue
  ↓
  elastic recoil pressure ↑
  ↓
  difficult to inflate the lung

Static compliance, V-P curve and hysteresis loop

00:17:08

V-P Curve



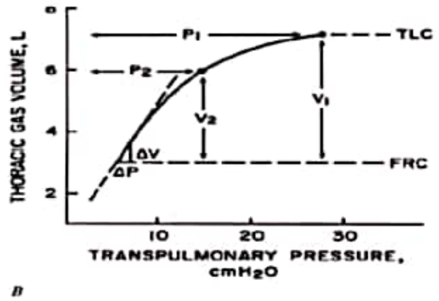
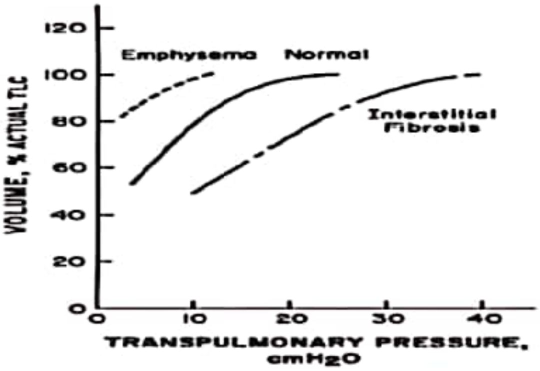


Figure 34-8 Measurement of the elastic properties of the lungs. *A.* Recordings of changes in lung volume and transpulmonary pressure (P_A-Ppl) using the esophageal balloon technique described in the text. Simultaneous measurements of volume and pressure are obtained during periods of arrested airflow at lung volumes ranging from total lung capacity (TLC) to just below functional residual capacity (FRC). *B.* Thoracic gas volume is plotted on the ordinate and transpulmonary pressure on the abscissa. The curve formed by the plot using values from *A* describes the elastic properties of the lungs. The slope of the line, ΔV/ΔP, over the range of the tidal volume is the static compliance of the lungs.

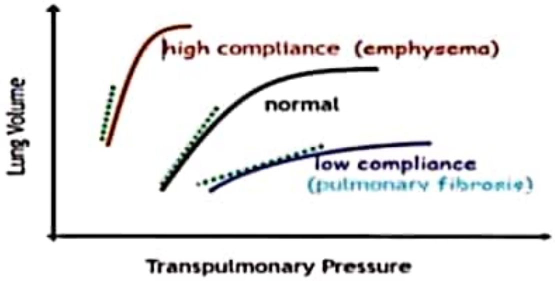
- Functional Residual Capacity (FRC)
  - → Amount of air in lung at end of normal expiration
  - → FRC = ERV + RV
- Slope = $\frac{\Delta V}{\Delta P}$ → static lung compliance
- Compliance is maximum for mid-range of pressures
- Normal static lung compliance = 0.2 L/cm of H_2O



- ↑ in elastic recoil pressure :
  - → Pressure curve shifts to right
  - → Compliance ↓
  - → Eg : Fibrosis

- ↓ In elastic recoil pressure
  - → Pressure curve shift to left
  - → Eg : Emphysema

STATIC COMPLIANCE OF THE LUNG
IS DETERMINED BY THE PV SLOPE AT FRC



- Compliance $\propto \frac{1}{\text{Elastance}}$

- Interstitial lung disease causes lung stiffness /opposes lung expansion and decreases compliance
  - → Curve shifts downwards and to right in Interstitial Lung Disease (ILD)

Hysteresis Loop

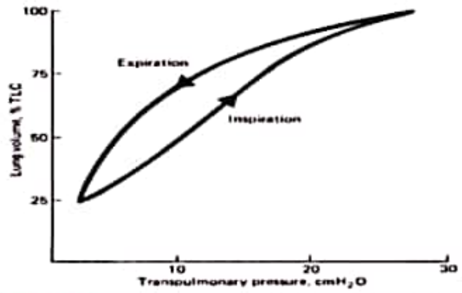


Figure 9-3 Pressure-volume curves of the lung during inspiration and expiration.

- In V/P curve, expiratory curve is at a higher level than inspiratory Curve → Hysteresis loop

- Difference between inspiratory and expiratory curve is due to :
  - → Surface tension (most important)
  - → Elastic recoil pressure difference

Equilibrium volume / relaxation volume

00:25:56

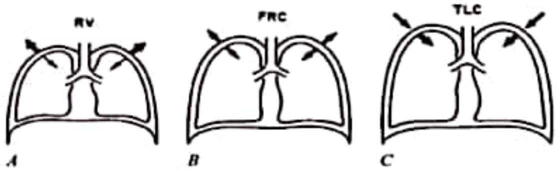
- At end expiratory position or FRC :
  - → Transpulmonary pressure = Elastic recoil pressure of lung
    = +5 cm of H_aO
  - → Transmural gradient across chest wall = −5 cm of H_aO
  - → They act equally in opposite direction

∴ FRC is called Equilibrium Volume / Relaxation Volume
  - At this point of FRC, tendency of chest wall to expand is equally counter balanced by tendency of the lung to collapse

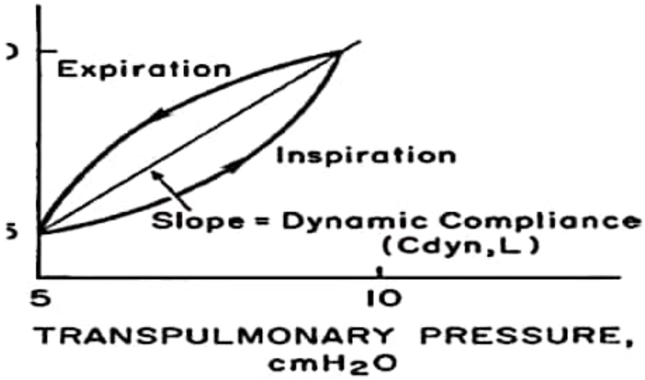
- tendency of lung to collapse is exactly equal to tendency of chest wall to expand (i.e elastic recoil of lung & chest wall are equal & opposite to each other)

- Distending Pressure = Transpulmonary Pressure
  = elastic recoil of pressure of lung

- Elastic recoil pressure = Elastic recoil pressure of lung + Elastic recoil pressure of chest wall



Dynamic compliance 00:38:09



- 3 opposing forces :
  - → Elastic force of lung tissue
  - → Surface tension
  - → Resistance

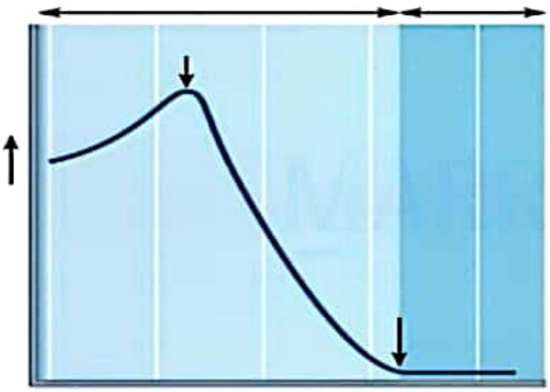
Warning : Not all points are covered in the notes, especially conceptual explanations. Please use the notes in conjunction with Marrow Edition 4 videos.

- Clinical conditions that decrease lung compliance :

Type of compliance :	clinical condition :	
→ Static compliance and dynamic compliance	• Atelectasis • ARDS • Tension pneumothorax • Obesity • Retained secretions	
→ dynamic compliance	• Bronchospasm • Kinking of ET tube • Airway obstruction	static compliance is normal

- Decrease in dynamic compliance : obstruction / bronchospasm
- Empysema – ↑ in static compliance and ↓ in dynamic compliance
  Resembles that of emphysema

Resistance and Fowler's curve



└→ plot of resistance

→ Resistance is maximum for medium sized bronchi (80%)

→ Lung volume is ↑ during expiration

→ Bronchial smooth muscle tone is mediated by :

- Leukotrienes (predominant)
- VIP (Vasoactive Intestinal Peptide)

- FVC can assess airway resistance

Fowler's curve :

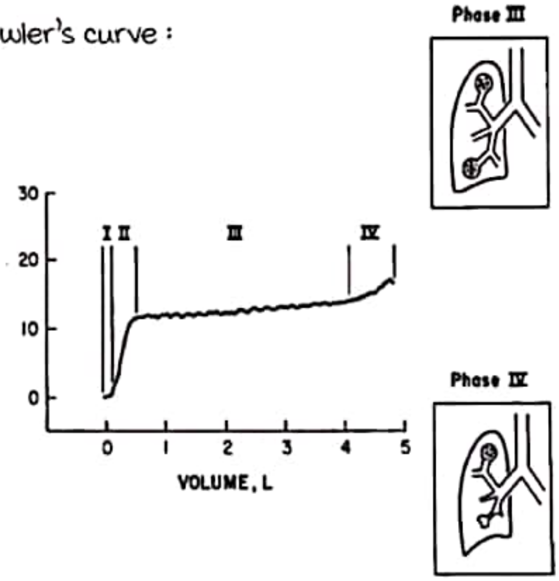


Figure 34-28 Contributions of different lung regions to the nitrogen concentration-volume curve obtained during the single-breath nitrogen washout test. See text for discussion.

- Test : single breath nitrogen washout test

↓

N_2 concentration in the expired gas

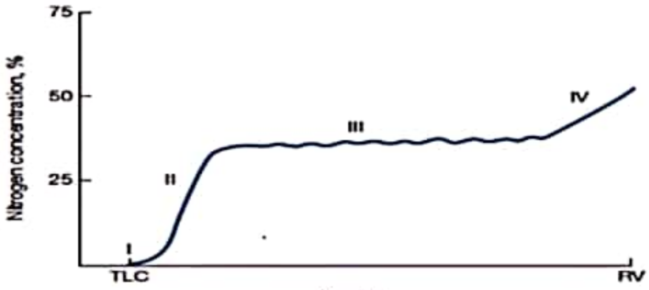
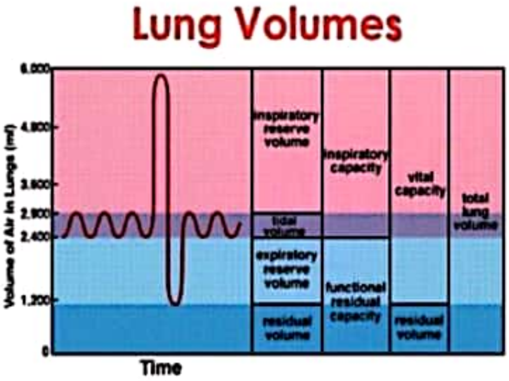


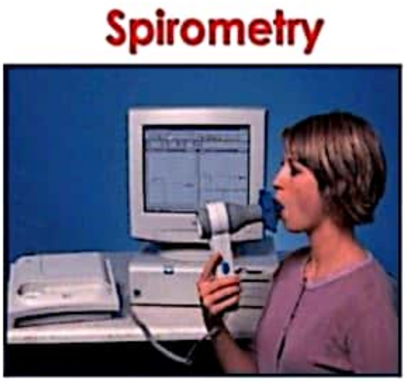
Figure 10-14 Tracing of expired nitrogen concentration during a slow expiration from TLC to RV after a full inspiration of pure O_2. The four phases are indicated.

- Phase I : dead space
  NO nitrogen
- Phase II : alveoli (predominant) + dead space
- Phase III : alveoli in mid-field and base (first to close)
- Phase IV : alveoli at apex (last to close)
  aka Closing Volume (normal closing volume is < 10%)
  - If closing volume > 10% of FVC → Small Airway Disease

Active space

Lung volumes 00:01:24


Lung Volumes


Spirometry

Volumes :

1. Tidal volume (TV) : Volume of air entering or leaving the lungs during a normal breath.
   - Normal : 500 ml (or) 6 – 8 ml/kg.
2. Inspiratory Reserve Volume (IRV) : By a forceful inspiration, the amount of air that can be breathed in above the tidal volume.
   - Normal : 1.9 – 3.3 liters (average: 3000ml)
   - males > Females
3. Expiratory Reserve Volume (ERV) : Above the tidal volume, the amount of air that can be expired out by a forceful expiration.
   - Normal : 0.9 – 1.3 litres (average: 1000ml)
   - males > Females.
4. Residual Volume (RV) : Amount of air in the lungs even after the most forceful expiration.
   - Normal : 1.2 litres.

Lung capacities 00:05:00

Capacities :

1. Inspiratory capacity (IC) = Tidal volume + Inspiratory Reserve volume.
2. Vital capacity (VC) / forced vital capacity : Tidal volume + Inspiratory Reserve volume + Expiratory Reserve volume.
   - Amount of air that can be forcefully exhaled after a maximum forceful inspiration.
   - 500 ml + 3000 ml + 1000 ml = 4 – 5 litres.
3. Functional Residual Capacity (FRC) : Amount of air in the lung after normal expiration.
   - FRC = Residual volume + Expiratory Reserve Volume
     = 1.2 + 1.0 litres

= 2 – 2.5 litres.

- FRC is almost 50 % of forced vital capacity.

4. Total lung capacity : TV + IRV + ERV + RV
= FVC + RV
= 5 – 6 litres.

- Spirometry cannot measure RV, FRC, TLC (total lung capacity)
- Lung Volume Calculation :
  - Determining FRC, TLC
    1. closed – circuit Helium method.
    2. Open – circuit Nitrogen wash out method.
    3. Total– body plethysmography – most preferred method.

↓

- most preferred method in gas trapping in airways / in peura
- FRC is also called as Equilibrium volume / Relaxation volume.
- At FRC, tendency of the lung to collapse is equally balanced by the chest wall to expand.
- Total Elastic Recoil pressure of system (lung + chest chest wall = zero
- Loss of Elastic Recoil pressure

↓

Hyperinflation

Body plethysmography

Functional residual capacity (FRC)

00:20:23

- FRC is high in emphysema
- High Elastic Recoil Pressure → ILD (interstitial lung disease) → FRC – low

Clinical Significance Of FRC

- **A high FRC (as in emphysema) means that when the patient is not breathing in, the lungs contain more air than normal.**
- **Breathing at that high lung volume helps prevent collapse of the airways and air trapping in emphysematous lungs, but at the same time, increases the effort of breathing. This can be very uncomfortable and can lead to dyspnea.**

- In Emphysema → FRC ↑ [hyperinflated] and airtrapping
(Dynamic compression of airways)

↓

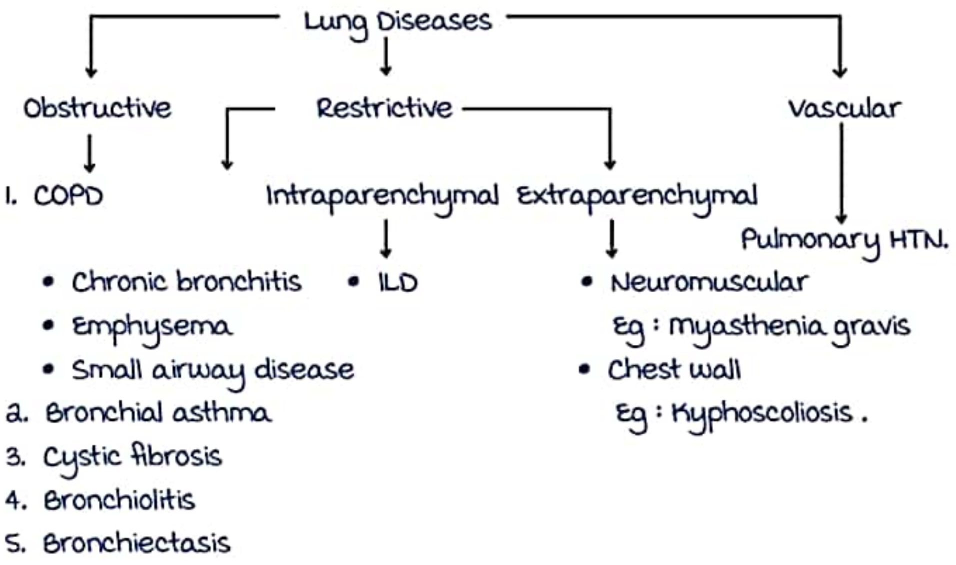
↑ effort of breathing

↓

Dyspnea.

Lung diseases

00:20:23

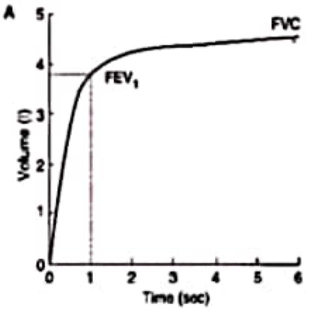

Lung Diseases
Obstructive
Restrictive
Vascular
1. COPD
Intraparenchymal
Extraparenchymal
Pulmonary HTN.
• Chronic bronchitis
• Emphysema
• Small airway disease
• ILD
• Neuromuscular
Eg : myasthenia gravis
• Chest wall
Eg : Kyphoscoliosis .
2. Bronchial asthma
3. Cystic fibrosis
4. Bronchiolitis
5. Bronchiectasis

Dynamic lung volumes

00:22:58

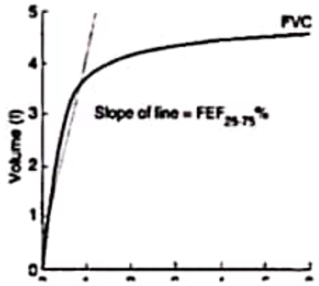
1. Forced Expiratory Volume in 1 sec [FEV_1] :

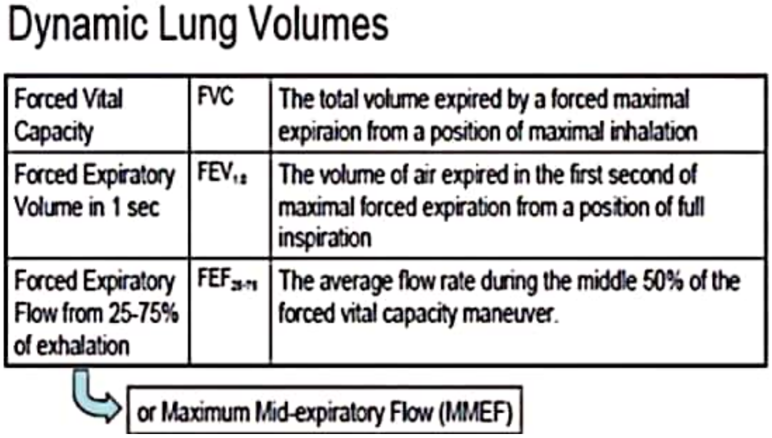
- volume of air forcefully expired from full inflation (Total lung Capacity) in the first second .
- measured in litres .
- normal people can exhale more than 75 – 80 % of their FVC in the first second; thus the FEV_1 / FVC can be utilised to characterize lung disease .



2. Forced Expiratory Flow 25 – 75% (FEF_{25-75}) :

- means forced expiratory flow during middle half of FVC .
- measured in liters / second .
- reflects effort independent expiration and the status of the small airways .
- depends heavily on FVC
- early termination artificially increases it .
- also called as maximum mid-expiratory flow rate .





Dynamic Lung Volumes

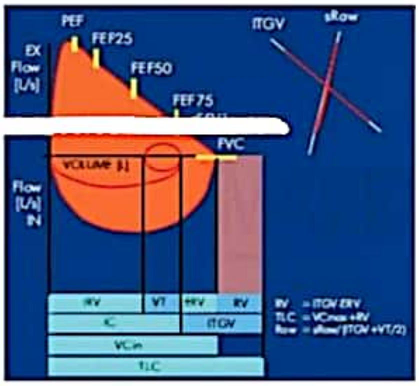
Forced Vital Capacity	FVC	The total volume expired by a forced maximal expiraion from a position of maximal inhalation
Forced Expiratory Volume in 1 sec	FEV_{1s}	The volume of air expired in the first second of maximal forced expiration from a position of full inspiration
Forced Expiratory Flow from 25-75% of exhalation	FEF_{25-75}	The average flow rate during the middle 50% of the forced vital capacity maneuver.

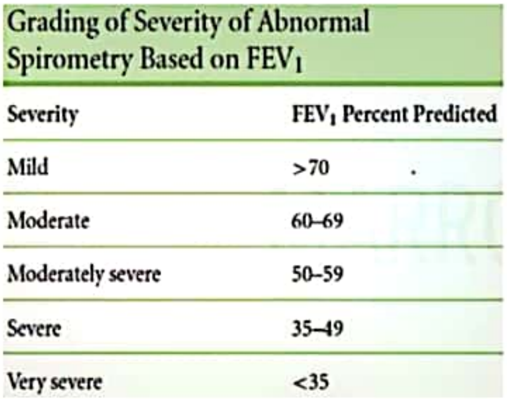
or Maximum Mid-expiratory Flow (MMEF)

Flow volume curve

00:32:03

- $\frac{FEV_1}{FVC}$ = > 80 % ⇒ Normal
- $\frac{FEV_1}{FVC}$ - < 80 % → Obstructive airway disease
- < 35 % - Very severe obstruction





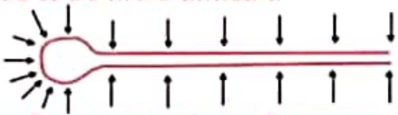
Grading of Severity of Abnormal Spirometry Based on FEV_1

Severity	FEV_1 Percent Predicted
Mild	>70
Moderate	60–69
Moderately severe	50–59
Severe	35–49
Very severe	<35

Dynamic airway compression

00:36:39

During inspiration the airways are pulled open by the expanding thorax. Therefore in cases of increased airway resistance expiration tends to be more difficult.

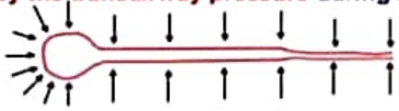


Transairway Pressure = Airway Pressure – Pleural pressure

The transairway pressure tends to compress airways during active expiration - pleural pressure rises during expiration (increases airway resistance)

If no obstruction: the increased airway resistance causes an increase in airway pressure upstream. This helps open the airways (i.e. reduce the compressive transairway pressure)

If there is an obstruction (e.g. COPD), the driving pressure between the alveolus and airway is lost over the obstructed segment. This causes a fall in airway pressure along the airways resulting in airway compression by the transairway pressure during active expiration.



- In COPD : Early stages : FEV_1 ↓, FVC - normal; late stage : FEV_1 ↓↓, FVC ↓

Obstructive airway pattern

Hyperinflation

- RV - increases with little or no change in VC
- TLC - increases proportional to RV (TLC > 120% of Predicted)
- FVC - maintained
- FRC - high
- RV - ↑↑
- TLC - ↑↑
- FEV1/ FVC : low

Air trapping

- Increase in RV with a proportional reduction in VC.
- TLC - constant (normally 80 - 120 % of predicted)
- FVC - low
- RV - ↑
- TLC - normal
- FEV1/ FVC : low

Restrictive airway condition

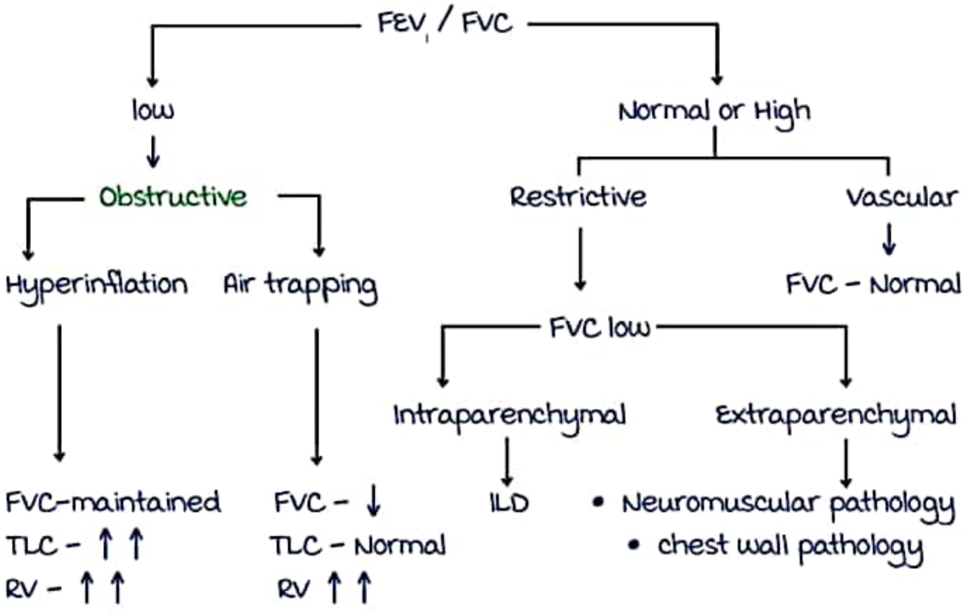
00:45:00

↑ Elastic recoil pressure

↓

low FRC

- If an intraparenchymal defect like ILD → low Residual volume and low TLC
- FVC → low
- $\frac{FEV_1}{FVC}$ → normal or High


FEV1 / FVC
low
Normal or High
Obstructive
Restrictive
Vascular
Hyperinflation
Air trapping
FVC – Normal
FVC low
Intraparenchymal
Extraparenchymal
FVC-maintained
TLC – ↑↑
RV – ↑↑
FVC – ↓
TLC – Normal
RV ↑↑
ILD
• Neuromuscular pathology
• chest wall pathology

FEF_{25-75} – small air way disease.

Respiratory membrane

00:50:00

- Diffusion coefficient of lung for carbonmonoxide [DLCO]

Respiratory membrane :

- Layer 1 : Fluid and surfactant
- Layer 2 : Alveolar epithelial layer.
- Layer 3 : Epithelial basement layer
- Layer 4 : Interstitial space
- Layer 5 : Capillary basement membrane
- Layer 6 : Capillary endothelial layer.
- Size : 0.2 – 0.5 micrometer / 70 m^2
- If diffusion gets affected

  ↓

  intraparenchymal pathology
- If diffusion is normal

  ↓

  Extraparenchymal pathology

Diffusion coefficient of lung for carbonmonoxide (DLCO)

00:52:39

DLCO : Volume of carbonmonoxide (CO) that diffuses across a gradient of pressure .

- measured in $\frac{\text{ml / minute}}{\text{mm Hg gradient}}$
- CO is used for DLCO because :
  - partial pressure in pulmonary capillaries rises very slowly in 0.75 seconds .
  - affinity of Hb for CO is 210 times more than O_2 .
  - its a Diffusion limited Gas .
  - all the 0.75 seconds at which blood is in contact with alveoli, CO is at a higher concentration in the alveoli than the capillary .
  - single breath hold test - for 10 seconds → Amount of CO in the exhaled air .

Factors affecting diffusion coefficient of lung for carbonmonoxide (DLCO)

00:55:16

Factors affecting DLCO :

1. Thickness of the membrane
   - Thick membrane ⟶ ↓ in DLCO Eg : ILD, smoking
2. Perfusion and capillary blood volume
   - Less perfusion → ↓ in DLCO Eg : Pulmonary hypertennsion (HTN)
3. Increased volume to surface area increase in volume to surface area ratio ⟶ Hyperinflated lungs ⟶ ↓ DLCO

   Eg : Emphysema
4. Hemoglobin available to accept that volume :

   Eg : anaemia, Pregnancy, pulmonary edema

Conditions with low DLCO :

- ILD
- Emphysema
- Pregnancy, anemia, smoking
- Pulmonary edema
- Pulmonary vascular disorders .

↑ DLCO .

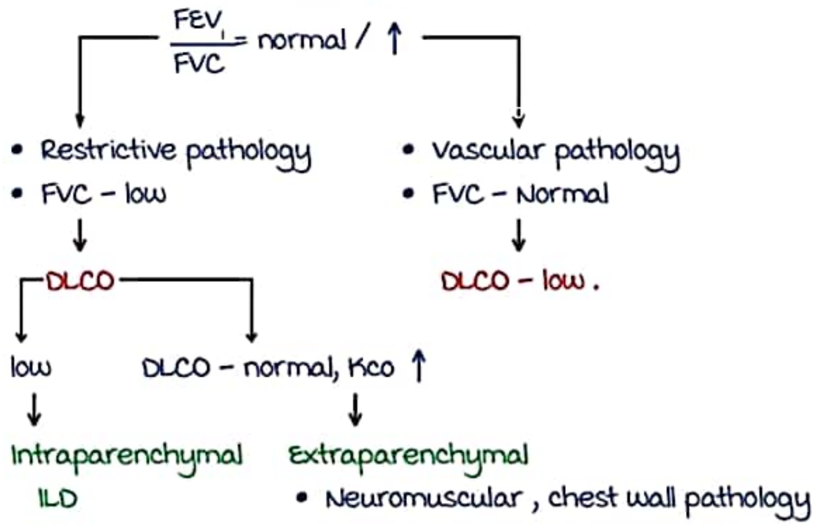
- Polycythemia
- Exercise
- Pulmonary vasculitis ⟶ diffuse alveolar Hemorrhage
- Left to Right shunting .
- Supine Position .
- mild congestive heart failure .
- Obesity, asthma

Transfer coefficient : Kco

$$Kco = \frac{DLCO}{\text{volume of air in the alveoli}}$$

Normally, Kco ↑ ⇒ DLCO ↑

- In Extraparenchymal pathology – DLCO – Normal but volume of air in the alveoli – ↓ → Kco ↑ .


FEV_1/FVC = normal / ↑

- Restrictive pathology
- FVC – low

↓ DLCO

low ↓ Intraparenchymal ILD

DLCO – normal, Kco ↑ ↓ Extraparenchymal

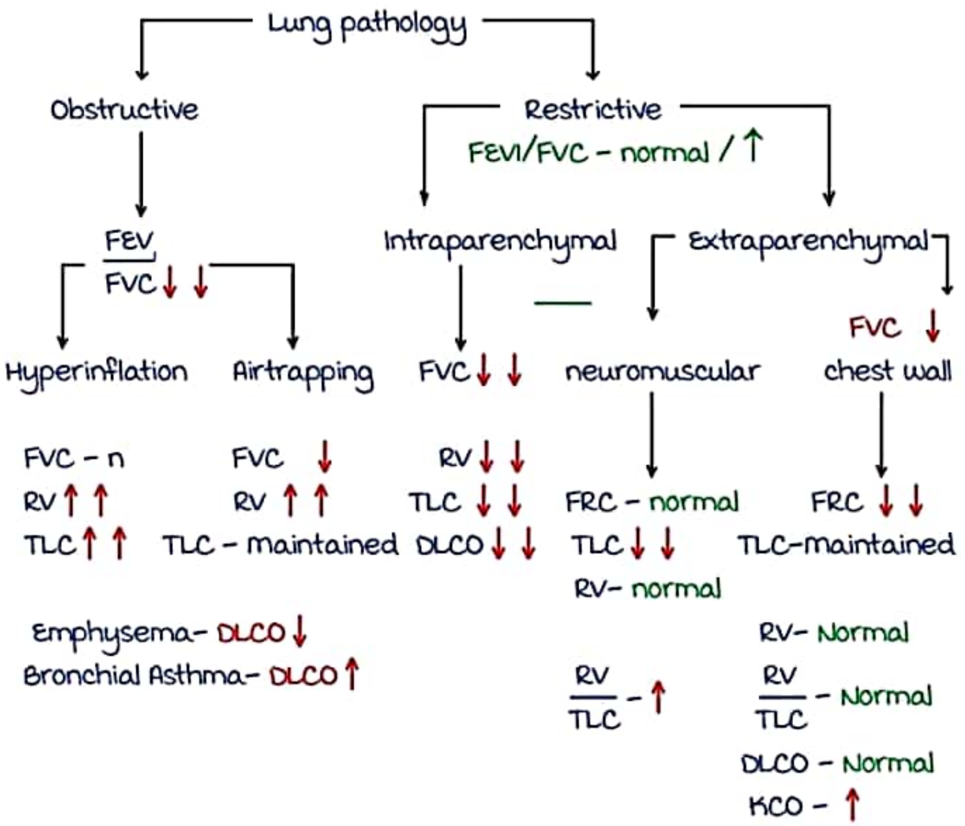
- Neuromuscular , chest wall pathology

- Vascular pathology
- FVC – Normal

↓ DLCO – low .

Lung pathology

01:03:32


Lung pathology

Obstructive ↓ FEV_1/FVC ↓ ↓

Hyperinflation: FVC – n, RV ↑ ↑, TLC ↑ ↑

Airtrapping: FVC ↓, RV ↑ ↑, TLC – maintained

Emphysema– DLCO ↓

Bronchial Asthma– DLCO ↑

Restrictive

FEV1/FVC – normal / ↑

Intraparenchymal ↓ FVC ↓ ↓, RV ↓ ↓, TLC ↓ ↓, DLCO ↓ ↓

Extraparenchymal

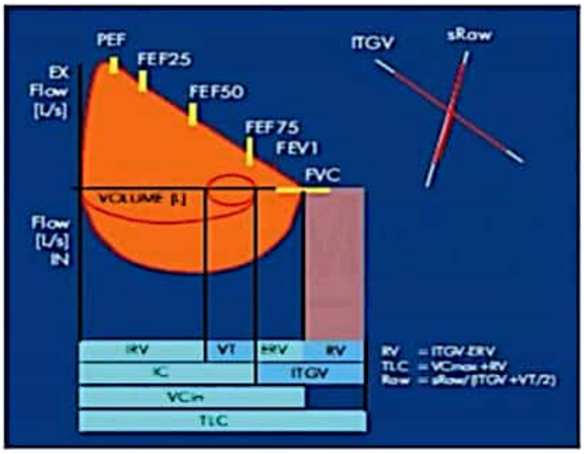
neuromuscular ↓ FRC – normal, TLC ↓ ↓, RV– normal, $\frac{RV}{TLC}$ – ↑

FVC ↓ chest wall ↓ FRC ↓ ↓, TLC–maintained, RV– Normal, $\frac{RV}{TLC}$ – Normal, DLCO – Normal, KCO – ↑

- Vascular pathology ⟶ FEV_1 / FVC – Normal / ↑
  DLCO – ↓

FLOW VOLUME LOOP

Normal flow volume curve :


PEF
FEF25
FEF50
FEF75
FEV1
FVC
EX Flow [L/s]
Flow [L/s] IN
VOLUME [L]
ITGV
sRaw
IRV
VT
ERV
RV
IC
ITGV
VCin
TLC
RV = ITGV-ERV
TLC = VCmax +RV
Raw = sRaw/(ITGV +VT/2)

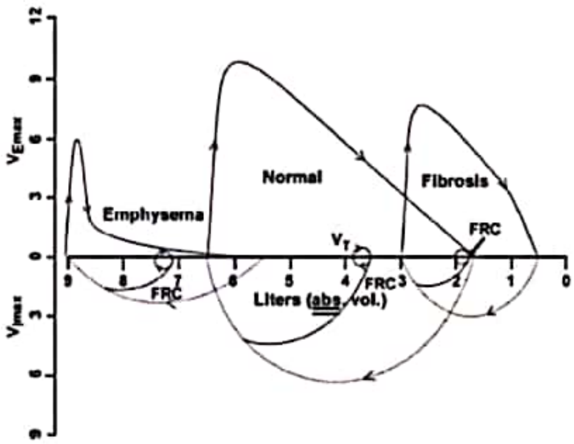
- Flow on Y – axis
- Volume on X axis
- Curve starts from Residual volume
- Inspiratory curve – saddle shape
- Expiratory part – has a peak (maximum flow = PEFR
  Peak expiratory flow rate)
- Ascending limb in expiratory part = effort dependent
- Descending limb in expiratory part = effort independent

Abnormal flow volume curve

00:02:21

Emphysema : obstructive condition

Obstruction pattern – Inspiratory part not affected
Expiratory part – ascending limb – architecture is near to normal
Descending part : more weak
K/a scooped pattern / dog leg pattern



Active space

Restrictive lung disease :
- Inspiration not upto TLC
  Expiration – normal
miniature of normal curve

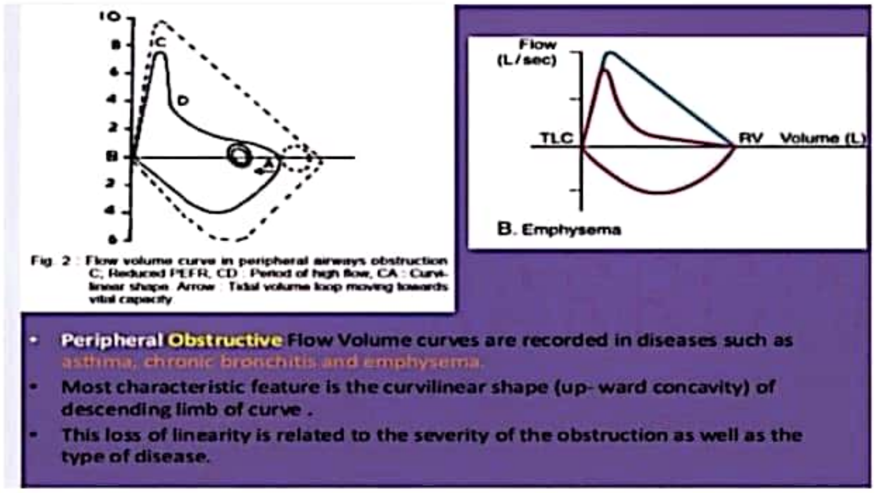
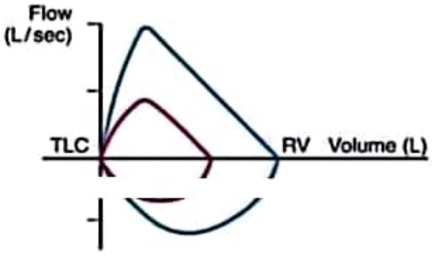


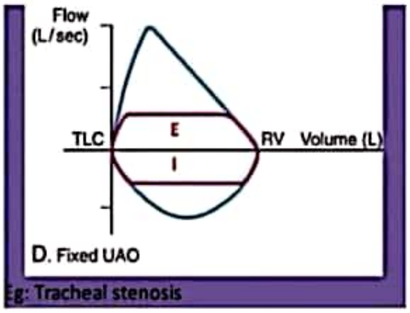
Fig. 2 : Flow volume curve in peripheral airways obstruction C; Reduced PEFR, CD : Period of high flow, CA : Curvilinear shape. Arrow : Tidal volume loop moving towards vital capacity

B. Emphysema

- Peripheral Obstructive Flow Volume curves are recorded in diseases such as asthma, chronic bronchitis and emphysema.
- Most characteristic feature is the curvilinear shape (up-ward concavity) of descending limb of curve .
- This loss of linearity is related to the severity of the obstruction as well as the type of disease.



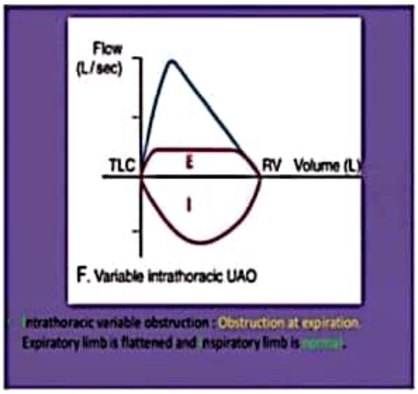
G. Restrictive parenchymal lung disease



D. Fixed UAO

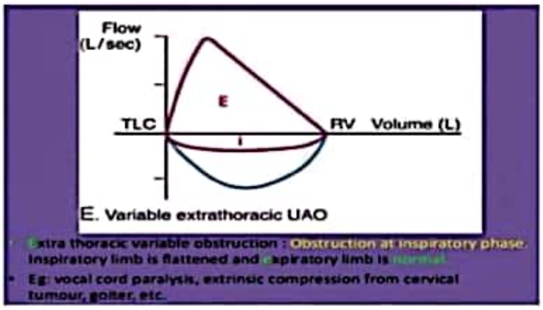
Eg: Tracheal stenosis

Fixed upper airway obstruction : tracheal stenosis
- both inspiration & expiration is equally affected



F. Variable intrathoracic UAO

Intrathoracic variable obstruction : Obstruction at expiration.
Expiratory limb is flattened and inspiratory limb is normal.

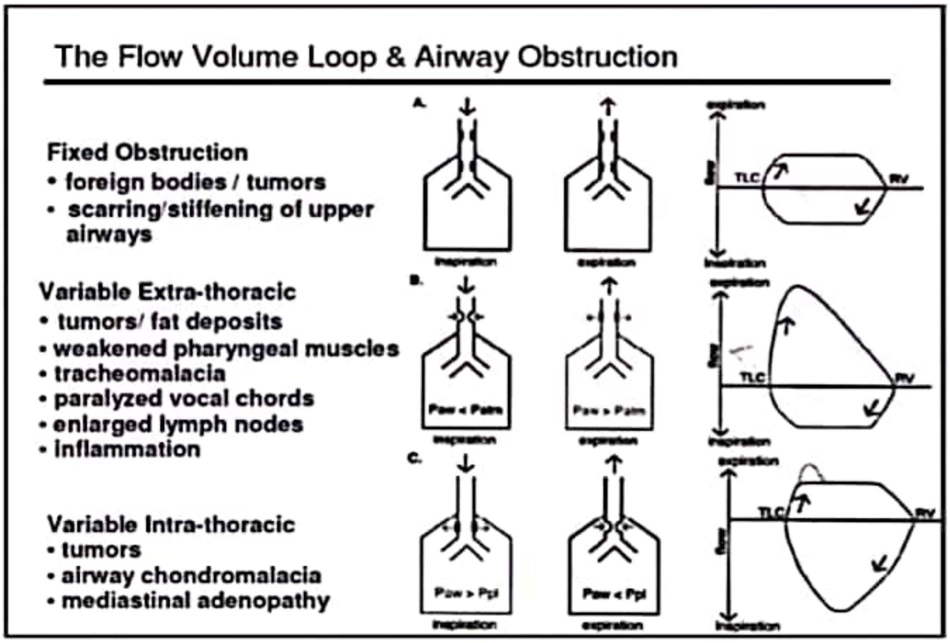


E. Variable extrathoracic UAO

- Extra thoracic variable obstruction : Obstruction at inspiratory phase.
  Inspiratory limb is flattened and expiratory limb is normal.
- Eg: vocal cord paralysis, extrinsic compression from cervical tumour, goiter, etc.

Active space

Variable intrathoracic obstruction : expiratory portion affected
Variable extra thoracic obstruction : inspiratory portion affected



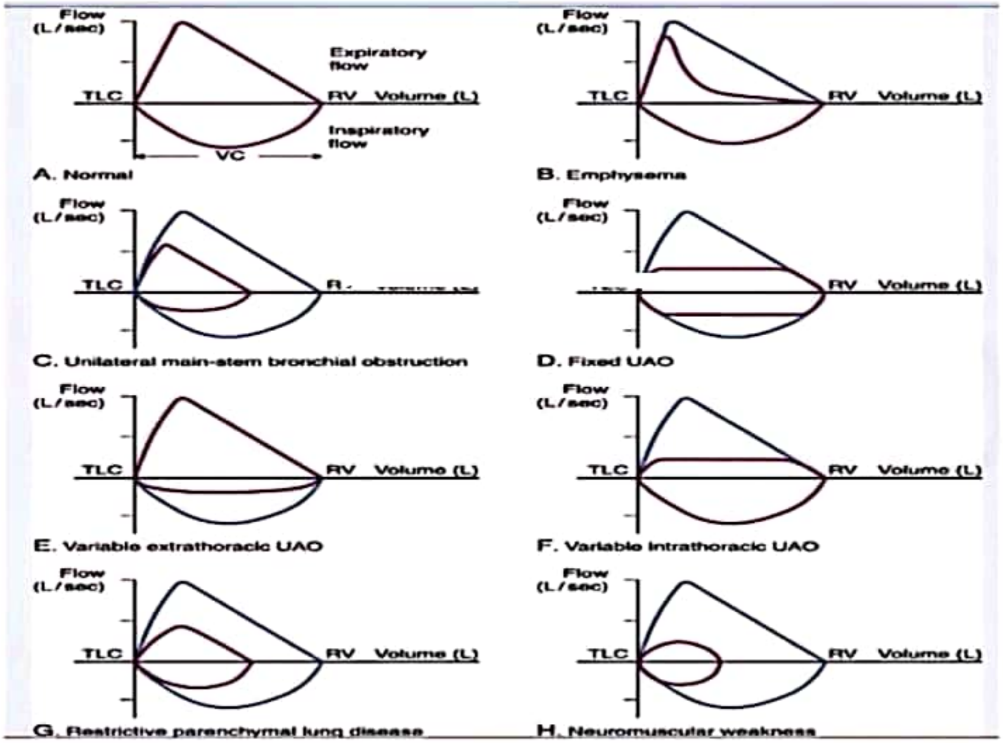
The Flow Volume Loop & Airway Obstruction

Fixed Obstruction
- foreign bodies / tumors
- scarring/stiffening of upper airways

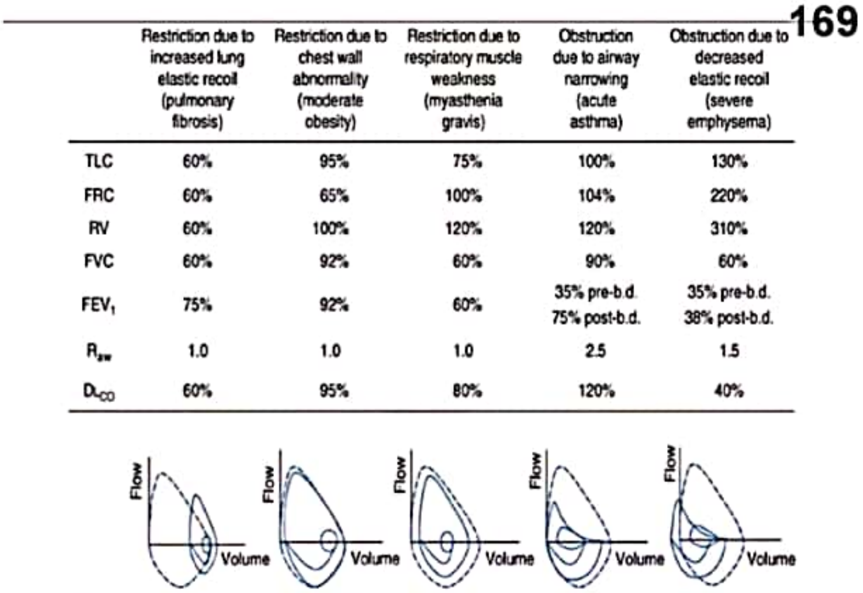
Variable Extra-thoracic
- tumors/ fat deposits
- weakened pharyngeal muscles
- tracheomalacia
- paralyzed vocal chords
- enlarged lymph nodes
- inflammation

Variable Intra-thoracic
- tumors
- airway chondromalacia
- mediastinal adenopathy

A.
expiration
flow
TLC
RV
inspiration
expiration
inspiration
B.
expiration
Paw < Patm
Paw > Patm
flow
TLC
RV
inspiration
expiration
inspiration
C.
expiration
Paw > Ppl
Paw < Ppl
flow
TLC
RV
inspiration
expiration
inspiration



A. Normal
B. Emphysema
C. Unilateral main-stem bronchial obstruction
D. Fixed UAO
E. Variable extrathoracic UAO
F. Variable intrathoracic UAO
G. Restrictive parenchymal lung disease
H. Neuromuscular weakness



169

	Restriction due to increased lung elastic recoil (pulmonary fibrosis)	Restriction due to chest wall abnormality (moderate obesity)	Restriction due to respiratory muscle weakness (myasthenia gravis)	Obstruction due to airway narrowing (acute asthma)	Obstruction due to decreased elastic recoil (severe emphysema)
TLC	60%	95%	75%	100%	130%
FRC	60%	65%	100%	104%	220%
RV	60%	100%	120%	120%	310%
FVC	60%	92%	60%	90%	60%
FEV_1	75%	92%	60%	35% pre-b.d. 75% post-b.d.	35% pre-b.d. 38% post-b.d.
R_{aw}	1.0	1.0	1.0	2.5	1.5
D_{LCO}	60%	95%	80%	120%	40%

Source: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J: Harrison's *Principles of Internal Medicine, 18th Edition*: www.accessmedicine.com

In obstruction – $\frac{FEV_1}{FVC}$ is ↓↓, TLC normal FVC ↓

RV ↑, FRC ↑ = airtrapping pattern / hyperinflation

ILD – $\frac{FEV_1}{FVC}$ = N / ↑, FVC ↓↓, DLCO ↓, RV ↓, FRC ↓

Neuromuscular – DLCO is normal, RV is normal, TLC ↓

$\frac{RV}{TLC}$ = ↑↑, KCO ↑

Kyphoscoliosis/ chest wall issue – DLCO is normal, RV normal, KCO ↑

TLC is normal, $\frac{RV}{TLC}$ = normal

Ventilation & perfusion

00:12:45

Ventilation (V) – maximum at the base (V_{max} = 4.2L/min)

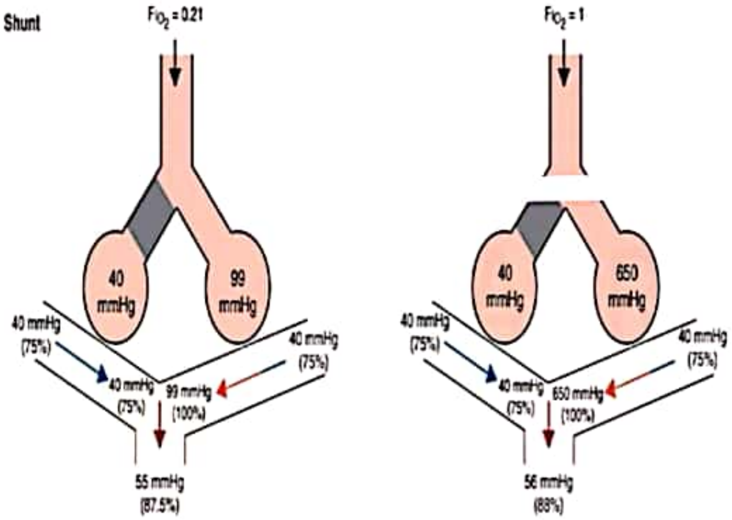
Perfusion (Q) – maximum at the base (Q_{max} = 5L/ min)

V/Q ratio– maximum at the apex

at base – 0.8

at apex – 3.3

Shunt physiology


Shunt
F_{IO_2} = 0.21
40 mmHg
99 mmHg
40 mmHg (75%)
40 mmHg (75%)
99 mmHg (100%)
40 mmHg (75%)
55 mmHg (87.5%)
F_{IO_2} = 1
40 mmHg
650 mmHg
40 mmHg (75%)
40 mmHg (75%)
650 mmHg (100%)
40 mmHg (75%)
56 mmHg (88%)

- Here blood is shunted from pulmonary artery to pulmonary vein, without being adequately oxygenated
- Total shunt physiology : Perfusion is normal, but has atelectatic alveoli, po2 reaching collapsed alveoli remains 40 mmHg or slightly ↑ to 55 mmHg even after oxygenation – severe failure
- Even with ↑ in FiO2, PO2 remains unchaged across a collapsed alveoli
  - shunting of blood +

v/q = zero

Partial obstruction (hypoventilated alveoli)
on ↑ FiO_2 po2 ↑ drastically k/a V/Q heterogeneity

Ventilation of unperfused alveoli : Dead space ventilation
V/Q = ∞

Ventilation volumes

00:19:21

Minute ventilation = tidal volume x respiratory rate
Alveolar ventilation = (tidal volume – dead space) x respiratory rate
Breathing reserve = maximum voluntary ventilation – minute ventilation
Physiological dead space = anatomical dead space + alveolar dead space

PULMONARY VASCULAR DISORDERS - 1

Pulmonary thromboembolism 00:01:38

→ Thrombi in pulmonary vasculature
→ Source of thrombi → Deep vein Thrombosis (DVT).
→ most common site for DVT → Deep veins of calf.
→ most common source of embolism → Popliteal > femoral vein.
→ In pregnancy → Pelvic veins.
→ Thrombi and microthrombi migrate from the systemic circulation into pulmonary vasculature.
→ Deep veins of lowerlimb > upper limb.

Risk factors:

- Genetic → most common → Factor V Leiden mutation
  → Protein C and protein S deficiency
  → Antithrombin III deficiency.
- malignancy → Adeno carcinoma
- Obstetric causes → Pregnancy, puerperium, HRT
- Nephrotic syndrome → membranous nephropathy
- COPD/ Congestive heart failure
- Surgery → with immobilization for more than 4days.
- APLA syndrome/ myeloproliferative disorders
  - Paroxysmal nocturnal hemoglobinuria.

Massive pulmonary embolism 00:07:12

- Pulmonary embolism with sustained hypotension or bradycardia (profound) → less than 40%

Submassive pulmonary embolism :-

- Pulmonary embolism without shock (hypotension)
- features of RV dysfunction diagnosed on Echo
- or elevated BNP
- or myocardial necrosis (Trop T or Trop I elevation)

Occlusion in the first order main pulmonary artery → symptomatic
70% occlusion or more → RV failure / hypotension
Hypoxia → Stimulate vagus → Bradycardia
Distal lodging of emboli (20%) → pulmonary infarction
Dead space ventilation = $\frac{V}{P} = \infty$ (infinity)

Symptoms of pulmonary embolism

- Acute onset dyspnea ± DVT
- Pleuritic chest pain is the second most common symptom
- Cough with hemoptysis in around 10%
- Tachypnea, tachycardia, chest clear → less than 10% will have crackles or decreased breath sounds
- Acute onset dyspnea within seconds.
- Chest pain in less than 20% → distal lodging of emboli
- Shock, S3, JVP → RV failure

Acute RV failure with hypotension/ S3
Hypoxemia/ respiratory alkalosis/ widening of alveolar-arterial gradient
Tachycardia more than transient ST/T changes
S1Q3T3 → Seen only in less than 10%
ECG finding → Tachycardia (m.c)
- transient ST/T changes.

S wave → in lead I
Q wave → in lead III
T inversion → in lead III

Rule out:
- RV Strain features
- T inversion in V1 - V4 (bad prognosis)

X-ray :- Normal in most cases
- long linear basal bands of atelectasis
- Pleural based opacities → "hamptons hump"
- Enlarged right descending pulmonary artery → Pallas Sign
- Focal oligemia of right lower lung → westermark Sign
→ Prominent central pulmonary artery → Fleischner sign

Wells score

Low probability (Low score)	moderate or high probability
• low	• high
• D - dimer - less than 500 ng/ml	• D- dimer not required • Helical CT pulmonary angiogram (IOC)
• PTE unlikely	• In Pregnancy → V/ Q scan

- Polo mint sign → Thin rim of contrast persists around a central filling defects due to thrombus

- Mc Connell's Sign → RV hypokinesia on ECHO.

Management of pulmonary embolism

00:25:33

- Non massive → Start anticoagulant at the earliest
  → Unfractionated heparin or low molecular weight heparin (Preferred) → 1 mg/kg SC BD.

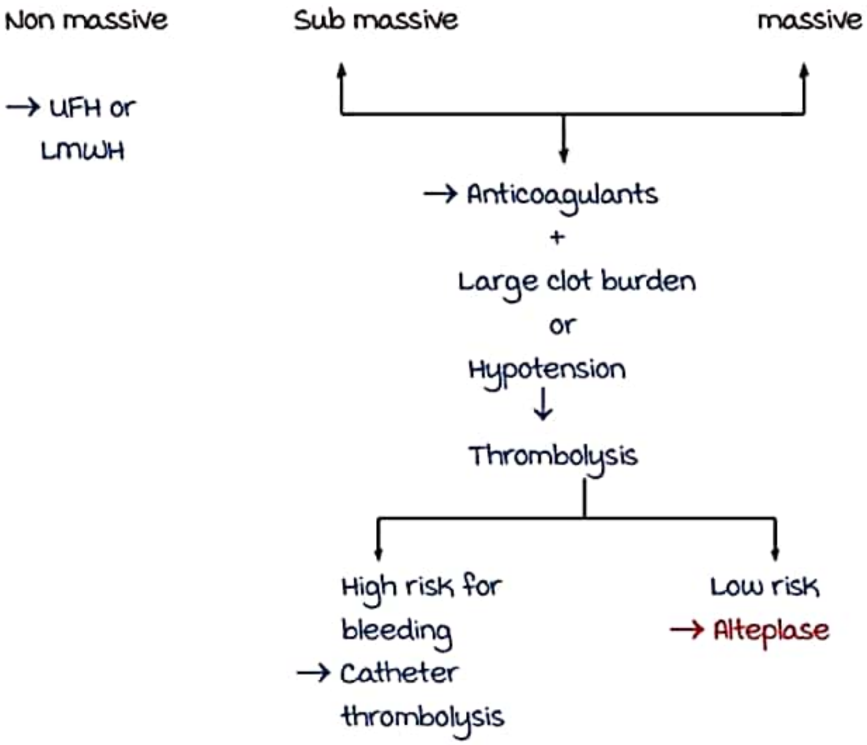
  Overlap with warfarin to maintain INR → 2 - 3

- In case of contraindication to anticoagulation : IVC filter.

- Submassive or massive thromboembolism (BP low)
  ↓
  with extensive Clot burden
  - Indication for thrombolysis.

  → Thrombolysis 2 types → medical thrombolysis
  → Alteplase 100 mg I.V for 2 hours
  → Catheter directed thrombolysis.

Warning : Not all points are covered in the notes, especially conceptual explanations. Please use the notes in conjunction with Marrow Edition 4 videos.


Non massive
→ UFH or LMWH
Sub massive
massive
→ Anticoagulants
+
Large clot burden
or
Hypotension
Thrombolysis
High risk for bleeding
→ Catheter thrombolysis
Low risk
→ Alteplase

Accessible emboli → Embolectomy

Active space

PULMONARY VASCULAR DISORDER - 2

Pulmonary Hypertension

00:01:00

WHO classification.

1) Primary pulmonary hypertension (idiopathic)
2) Due to left heart failure
3) Due to chronic lung disease with hypoxia
4) Chronic thromboembolic pulmonary HTN
5) miscellaneous (Compression of pulmonary artery)

Definition – mean pulmonary artery pressure > 25 mmHg

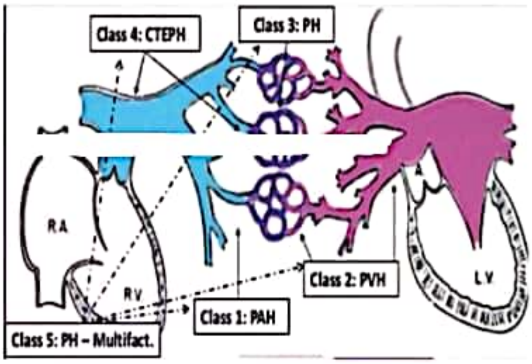
RVH + dilatation = RV failure – Cor pulmonale

$$\text{Pulmonary vascular resistance} = \frac{\text{Rt side pressure} - \text{Lt side pressure}}{\text{Cardiac output}}$$

Class I PVR > 3 Wood units
Class II PVR < 3 Wood units

Sites of lesion

00:05:57



I – pulmonary artery
II – pulmonary vein
III – pulmonary capillary
IV – Artery + precapillary

Group I pulmonary artery hypertension (PAH)

1) Idiopathic
2) Heritable → mutation in BMPR 2 gene
(bone morphogenic protein receptor)
3) Drugs.
   - Toxic Fenfluramine
   - Rapeseed oil

4) Autoimmune – Limited scleroderma
CREST syndrome
5) HIV and schistosomiasis

Pathophysiology of PAH 00:09:31

1) Underexpressioin of NO → ↑ Endothelin – 1
2) Remodelling of vessel wall
3) Thrombosis in situ

T_x
- ET – 1 antagonists
- PDE inhibitors
- ↑ No (by ↑ cGMP) / prostacyclin

Clinical features
- No specific symptoms
- Breathlessness without overt signs of heart and lung disease with fatigue
  ±
  syncope
- Chest pain
- Features of right heart failure(RHF)

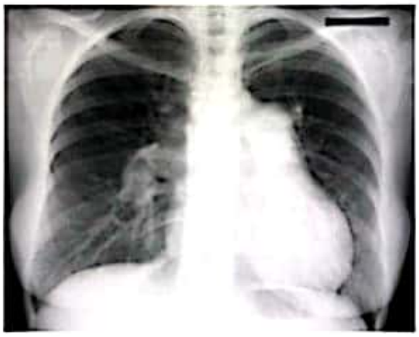
Sign
1. 'a' waves on JVP
2. Clear lungs
3. Hepatomegaly, Edema, cold extremities .
4. A_2–loud P_2 →mild
   Loud P_2 → moderate to severe
   Loud P_2 with A_2 – P_2 hidening – RVF
5. Palpable epigastric impulse / left parasternal heave .
6. Right ventricle S_3

Gold standard for diagnosis – pulmonary artery catheterisation .

Murmurs in PAH 00:17:03

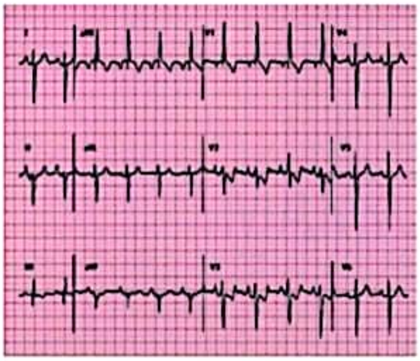
1. Tricuspid regurgitation – High pitched holo / pan systolic soft blowing murmur ,along the left lower sternal border
   ↑ on inspiration (Carvallo's sign)
2. Pulmonary stenosis – Ejection systolic murmur

3. Severe PAH – High pitched EDM due to pulmonary artery dilatation with associated Pulmonary regurgitation in sitting and leaning position (Graham – steel murmur)



X- Ray findings in PAH
- Large central pulmonary artery
- Rapid tapering of vessels
- Clear
- RVH

ECG finding in PAH

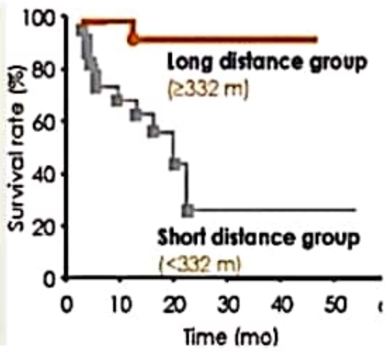


- $\frac{R}{S} > 1$ in V_1
- RVH
- RAD

Other invesigations in PAH

00:20:25

1. PFT → $\frac{FEV_1}{FVC}$ Ⓝ Diffusing capacity of lung for carbon monoxide ↓↓
2. DLCO ↓↓
3. Polysomnography – OSAS → PHTN
4. ECHO – RV function and TR
5. CT chest – rule out ILD
6. V/Q scan
   ↓
   Chronic pulmonary thromboembolism



Prognostic test in PAH

1) 6 minute walk test

2) Vasoreactivity test with inhaled nitric oxide
↓
MAP in PA falls by 10 mmHg
With preserved cardiac output
↓
Positive
↓
indication for CCB in PAH

Active space

Treatment of PAH

00:24:17

I Supportive
  1) 240mg nifedipine only if vasoreactivity +
  2) Pregnancy must be avoided
  3) oral ar [illegible]
  4) Long term oxygen therapy
  5) Diuretics for RHF

II PAH specific therapies
  1. CCB → 240mg nifedipine
  2. Endothelin antagonists (DOC) – Bosentan
     Ambrisentan
  3. PDE – 5 inhibitors – Sildenafil
     Tadalafil
  4. Prostanoids

Via syringe pump onto pulmonary tunneled catheter	Epoprostenol
Continuous subcutaneous infusion via micro infusion pump	Treprostinil
First chemically stable and orally active prostacyclin derivative	Beraprost

III surgical Atrial septostomy
↓
Transplant

- Pulmonary endarterectomy is most successful when done in class IV PAH

BRONCHIECTASIS

Bronchiectasis - Introduction 00:00:44

→ Abnormal, irreversible dilation of bronchi

→ Destruction of smooth muscle and elastic tissue due to :
  - Infection
  - Congenital
  - Autoimmune

→ Impaired mucociliary clearance
↓
prone for infection

→ Obliterative fibrosis of bronchioles

→ 30% bronchiectasis – idiopathic

→ Left lobe → most commonly involved

→ more common in females than males

→ 50–70 years

Types of Bronchietasis :

- Cylindrical or tubular : most common and bilateral
- Varicose
- Cystic → childhood infections
  - measles and whooping cough
  - Clubbing present
- Traction Bronchiectasis → restrictive
  - ILD
  - Fibrosis

Change seen in bronchiectasis :

1. Loss of cilia
2. Increased mucus
3. Destruction of cartilagenous wall

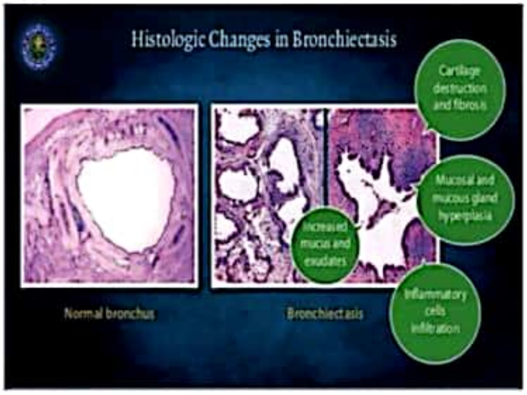
Histological changes in Bronchiectasis 00:06:43

- Cartilage destruction and fibrosis
- Mucosal and mucus gland hyperplasia
- Increased mucus and exudates
- Inflammatory cells infiltration

Active space

Causes for bronchiectasis :

1. Post infective
   - Child → measles, pertusis
   - Adult → mycobacterium TB
   - Obliterative bronchiolitis due to infection in childhood
     → mcleods syndrome



Histologic Changes in Bronchiectasis

Cartilage destruction and fibrosis
Mucosal and mucous gland hyperplasia
Increased mucus and exudates
Inflammatory cells infiltration
Normal bronchus
Bronchiectasis

2. Obstruction
   - Right middle lobe obstruction due to lymph node (secondary to tuberculosis)

     ↓

     Right middle lobe bronchiectasis
     - Brochs syndrome

Infections causing middle lobe bronchiectasis
- Non tuberculous mycobacterium

3. Immunodeficiency → common variable immunodeficiency
   - Isolated Ig A deficiency

4. Impaired mucociliary clearance
   - Kartagener's syndrome
   - Cystic fibrosis
   - Young's syndrome (azoospermia)

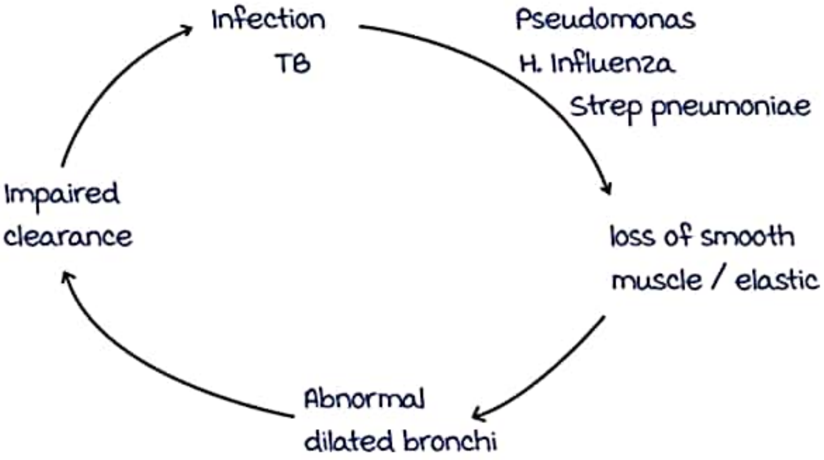
5. Autoimmune → Sjogren syndrome

Congenital syndrome associated with bronchiectasis 00:10:36

- Mounier Kuhn → Tracheobronchomegaly
- William campbell → absence of cartilage
- Kartagener's syndrome
- Youngs syndrome
- Yellow nail syndrome
- Cystic fibrosis
- Alpha 1 antitrypsin deficiency → Liver + panacinar emphysema

→ All of them involve middle lung fields

Pathogenesis :


Infection
TB
Pseudomonas
H. Influenza
Strep pneumoniae
loss of smooth muscle / elastic
Abnormal dilated bronchi
Impaired clearance

- Chronic cough with excessive expectoration
- Foul smelling sputum
- Hemoptysis with streaks of blood
- Acute pneumonia exacerbation

Symptoms of bronchiectasis

00:14:07

- Chronic cough with expectoration of mucopurulent sputum with episodes of acute exacerbation
- Hemoptysis with streaks of blood
- Recurrent pneumonia – rule out underlying bronchiectatic lobe .

Signs :–

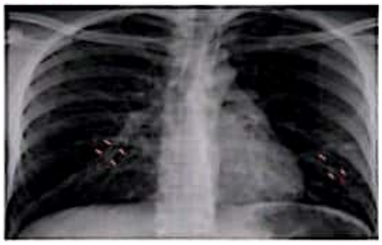
- Clubbing
- Early and mid inspiratory coarse crackles + diffuse rhonchi

- Dry bronchiectasis (sicca) seen with tuberculosis
- Central or proximal bronchiectasis is associated with Allergic Bronchopulmonary aspergillosis Bilateral
- Right middle lobe bronchiectasis → Brochs syndrome

Diagnosis :

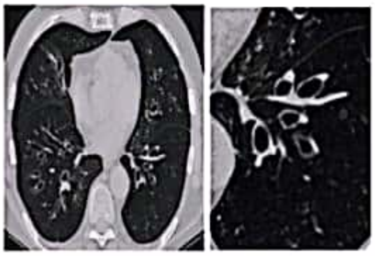
X– Ray – dilated bronchial walls → Tram track lines
- Finger in glove appearance → ABPA
- Bunch of grapes appearance

Volumetric multi detector helical CT scan .



Active space

1. Airway diameter more than 1-1.5 times adjacent vessel → signet ring sign
2. Absence of bronchial tapering
3. Tree in bud pattern
4. Nodular opacities due to mucus filled bronchi



- Central distribution, upper lobe, fibrotic bands → ABPA

Complications:

- massive hemoptysis
- Empyema with bronchopleural fistula
- cor pulmonale
- Lung abscess
- Secondary amyloidosis

Treatment of bronchiectasis 00:20:01

- Airway clearance with physiotherapy and postural drainage is the cornerstone of therapy.
- Nebulized 7% hypertonic saline or steam inhalation to clear secretions.
- Airway clearance with cough assisted devices like flutter valves.
- Recombinant human DNAse for cystic fibrosis associated bronchiectasis
- Resection → localized bronchiectasis with recurrent infection unresponsive to drugs

Antibiotics for bronchiectasis:

- Nebulized gentamicin as prophylaxis in cystic fibrosis to reduce frequency of exacerbation
- Infection → drug that reaches effective concentration within lung and bronchial mucosa
  → β lactams, macrolides
- macrolides have immunomodulatory action and are recommended for 6 - 9 months.

Pneumoconiosis

00:00:43

- Accumulation of dust in the lungs and the tissue reactions in response to that
- 1 -5 micro metre size.

1. Silicosis (m.c)
2. Asbestosis
3. Coal workers pneumoconiosis
4. Byssinosis

Asbestosis:

- Asbestos fibers → serpentine / chrysotile → 90%
  - Curly strands
  - not toxic
- Amphibole → 10%

Crocidolite   Amosite

- long, Straight, rod like Structure → Toxic

→ Textile, ship building, Cement industry

→ more than 10 year exposure is mandatory

Pleura involvement: most common involved

→ Benign pleural plaques. (m.c.)

→ Earliest manifestation: BAPE
(Benign asbestos related pleural effusion)
↓
Characterised by the presence of mesothelial cells, Bloody, effusion Eosinophilic

Pleural plaques → Diffuse pleural thickening →
→ Fibrosis with calcification.

X - Ray findings:

- Holly leaf Sign → Thick calcified pleural plaques
- "Shaggy heart border Sign" → Obscure heart borders

malignancy with respect to asbestosis:

- Asbestos related lung Carcinoma
- Asbestos related plural mesothelioma.

Asbestos related lung Carcinoma	Asbestos related pleural mesothelioma
Latency → 20 - 25 years	more than 30 years
• Adeno or squamous or Small cell carcinoma	• Epitheloid type (m.c.)
• Smoking multiplies the risk	• Smoking is not associated.
• Cough and hemoptysis	• Chest pain (pleuritic or mass detected on X - ray)
• EGFR mutation	• Pancytokeratin, Calretinin.
	• Electron microscopy Findings : - Microvilli - Tonofilaments - Desmosomes.

Lung parenchyma involvement :

→ Seen usually after 10 years

→ Bilateral and lower lobe involvement

→ manifestation- B/L infiltrates with plaques

→ Progresses to fibrosis → Diffuse massive fibrosis

↓

Exertional dyspnea

↓

Typical restrictive pattern on PFT

- Subpleural fibrosis of lower lobes of the lung
- Asbestos bodies with a transparent core Surrounded by iron and protien → Ferruginous bodies
- Bi basal fine respiratory crackles and clubbing may be present.

Silicosis 00:21:31

- Active molecule → free silica or silicon dioxide
  - Crystalline (Quartz) most dangerous,
  - Amorphous
- Rock, Slate, granite, sandstone

→ Tendency to injure pulmonary alveolar macrophages.

high incidence of active TB in patients with silicosis
→ Nocardiosis involved.
→ Bilateral symmetrical upperlobe involvement.

Acute Silicosis	Chronic Silicosis
• manifests within 2 years.	→ Involves lung parenchyma
• Severe dyspnea with hypoxemia	
• DD → Pulmonary alveolar proteinosis	
• PAS positive milky white BAL.	
• CT → Bilateral centrilobular nodules and ground glass opacification.	

→ Crazy pavement pattern : – pulmonary alveolar protienosis
(more specific)
– Acute Silicosis

Chronic silicosis :
→ 10 – 30 years of silica exposure.
→ Asymptomatic
→ Chronic cough with progressive dyspnea on exertion
→ mixed obstructive restrictive pattern.
. Nodules → Small nodules → Large nodules
↓
conglomerate nodules
→ Involves upper zone.
→ Associated with hilar adenopathy
→ Egg shell Calcification
→ Progressive massive fibrosis > 1 cm nodules

- Chest Signs → in 25 %
  → Bilateral inspiratory crackles
  → Clubbing very rare
- Hilar retraction with upper lobe fibrosis.
- Cavitation may be present → Silico tuberculosis
- Numerous sharply marginated small sized nodules in upper lobe / Hilar lymph node

Coal Workers Pneumoconiosis 00:35:20

↓ Simple Coal workers pneumoconiosis
↓ Complicated Coal workers pneumoconiosis
↓ Caplans Syndrome

→ Black lung on exposure to coal dust

Simple coal workers pneumoconiosis :

- → Small , round opacities or nodules in the upper zone without lung impairment
- → may lead on to COPD
- → Larger nodules more than 1 cm in upper lobe with hilar adenopathy, Cavitation , not much calcification

↓

upper lobe fibrosis → progressive massive fibrosis

Caplan's apostrophy syndrome

- → Seropositive Rheumatoid arthritis
- → Complicated coal worker pneumoconiosis (Cavitating nodules or necrobiotic nodules)

Byssinosis 00:39:42

- → Cotton factory workers
- → Fever , dyspnea and chest tightness especially on the first day of work after weekend
  - → monday chest tightness
- → Producing bilateral infiltrates predominantly : Lower lobe
- → CT → Nodules with ground glass opacification

Berylliosis 00:43:00

- → Alloys , ceramics industry workers
- → Similar to Sarcoidosis → non caseating granulomas
- → Dypnea
- → upper lobe interstitial lung disease
- → Nodules
- → Lymphocyte proliferation test → positive

ARDS

ARDS 00:04:30

aka Shock lung
- Acute lung injury
- Alveolar injury
- Diffuse alveolar damage
- Blast lung

Fluid in alveoli and interstitium

↓

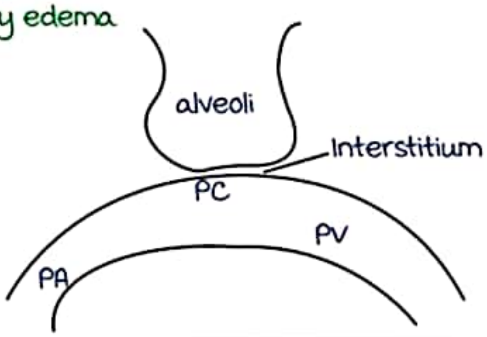
Pulmonary edema

↓ Cardiac cause

↓ Non - cardiogenic → ↓ ARDS

Factors preventing pulmonary edema

1) Increased intravascular protein
2) Very efficient interstitial lymphatics
3) Tight junctions between alveolar epithelical cells.



PV - Pulmonary vein
PA - Pulmonary artery
PC - Pulmonary capillary

major - Alveolar epithelial injury

Pathophysiology of ARDS 00:10:04

Alveolar epithelial injury

↓

IL - 1, TNF - α, IL - 6

↓

Recruit neutrophils and damage of capillary endothelium

↓

Fluid coming out of endothelium

↓

pulmonary edema

↓
ARDS

- impaired gas exchange (Type I resp failure)
  ↓
  Hypoxia → Dyspnea
  ↓
  pulmonary vasoconstriction
- pulmonary vasoconstriction
- ↓ lung compliance (Type 3 resp failure)
  Epithelial damage
  ↓
  air spaces filled with bloody proteinaceous Fluid
  ↓
  Loss of surfactant
  ↓
  collapse
  (ie ↓ compliance)

Causes Of ARDS

00:13:28

Direct lung injury	Indirect lung injury
1. Acute lung infection	1. Sepsis (MCC) due to pneumonia
2. Aspiration pneumonia	2. Acute pancreatitis
3. Drowning	3. massive blood transfusion
4. Chemical inhalation	4. Post CABG
	5. Trauma
	6. Burns

Clinical features of ARDS

00:19:41

1. Dyspnoea of rapid onset
2. Hypoxemia → Type I respiratory failure
3. Tachypnea, Diaphoresis, Tachycardia
4. Infiltrates on X-ray
   Bilateral crackles

5. Phases : $(A - a) O_2$ gradient ↑

0 - 7 days	Exudative
7 - 14 days	Fibroproliterative
>14 days	Fibrotic

Criteria For ARDS

00:22:1

Earlier used / obsolete criteria

1. Acute Onset (<1 week)
2. B / L interstitial / alveolar infiltrates
3. PCWP ≤ 18 mmHg
   (Indicates left atrial pressure)
4. $\frac{PaO_2}{FiO_2}$ ratio (< 300 mmHg)
   ↓
   200 – 300 mmHg mild (acute lung injury)
   100 – 200 mmHg moderate
   <100 mmHg Severe

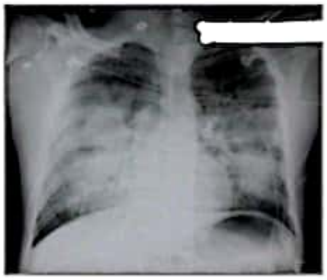
Berlin's criteria

- Acute onset (< 1 week)
- B/L intertitial / alveolar infiltrates
- PCWP ≤ 18 mmHg , Exclude cardiac cause
- $\frac{PaO_2}{FiO_2}$ ratio same , Acute lung injury – removed this term
- with a PEEP of >5cm of H_2O

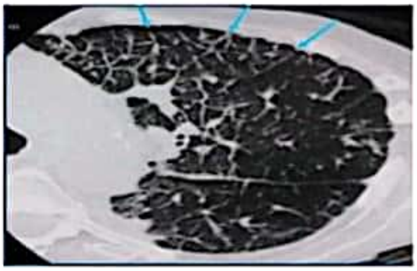
Signs Of Ards

00:28:04

1. Bat wing appearance
   seen in pulmonary edema



2. Interlobular septal thickening
   - K/a Kerley B lines
   - Perpendicular to pleura



Features suggesting cardiogenic pulmonary edema

1. S_3 / S_4
2. JVP elevation
3. Kerley B lines
4. BNP

1. Nasocomial pneumonia
2. Sepsis / MODS
3. GI bleeds
4. Critical illness polyneuropathy

Management Of ARDS

1. High frequency low tidal volume with high PEEP

↓

K/a Inverse ratio Ventilation

(Inspiration > expiration)

2. Prone Ventilation
3. Permissive hypercapnia

EOSINOPHILIC LUNG DISEASES

Pulmonary eosinophilia

00:02:57

- aka eosinophilic lung diseases
- Eosinophils in airway / lung parenchyma
  - a) Either lung tissue eosinophilia
    or
  - b) BAL eosinophilia
    or
  - c) Peripheral blood eosinophilia with infiltrates on X ray.

Pulmonary infiltrates with eosinophilia (MC used term)

Causes

1. Parasite
2. Vasculitis → Allergic granulomatosis polyangiitis, Churg strauss syndrome / Eosinophilic granulomatosis with polyanggiitis, Sjogren's syndrome
3. Acute eosinophilic pneumonia
4. Chronic eosinophilic pneumonia
5. ABPA (Allergic Bronchopulmonary aspergillosis)
6. ILD
   - a) Cryptogenic organism pneumonia (COP)
   - b) Langerhans cell histiocytois (LCH)

Not

1. Hypersensitivity pneumonitis (HSP)
2. Pulmonary eosinophilic granuloma.

BAL with eosinophilia

00:08:35

BAL > 40 % eosinophils

1) Chronic eosinophilic pneumonia
2) Tropical pulmonary eosinophilia

Parasite

Loeffler's syndrome

Ascariasis > Ancylostoma > strongyloides
(MCC)   Necator
↓
Infective (rhabditiform larvae)

Penetrates into alveoli, matures and ascends into airways

Active space

↓

Type I hypersensitivity reaction

↓

Asthma / children – Cough
Substernal discomfort
Wheeze
migratory infiltrates

↓

No treatment required
very good prognosis

Lung fluke

00:14:30

- Paragonimus westermanii

metacercaria
↓ mature
Adult worm in the lung
↓
Invasion of lung
↓
1) Cavitating nodules – Chocolate colored sputum
2) Eosinophil rich pleural effusion
3) CT → nodules with ground glassing
↓
Diagnosis – Egg in sputum
ELISA

DOC – Praziquantel

Tropical pulmonary eosinophilia

00:17:36

- microfilaria (in blood)

↓
Type I Hypersensitivity in lungs.

- m>F
- Gradual onset of symptoms – Cough, wheeze (night)
  – systemic weight loss
  Hepatosplenomegaly

↓

eosinophilia , increase in IgE , antifilarial antibodies +

- miliary mottling on X ray
- mixed pattern on PFT → ↓ DLCO

R_x – DEC 6 mg/ Kg for 21 days.

Drugs causing lung infiltrates with eosinophilia

1. NSAIDS
2. Nitrofurantoin
3. Minocycline
4. Ampicillin
5. L tryptophan/rapeseed oil

Acute eosinophilic pneumonia 00:22:30

- Young males
- Smokers (Symptoms after restarting smoking)

↓

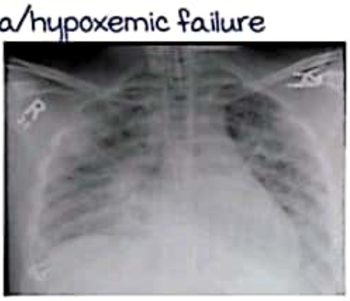
Acute onset respiratory failure

Clinical features

→ Fever/non productive cough /tachypnoea/hypoxemic failure

→ Diffuse parenchymal opacities

→ No systemic features



Peripheral smear → ± eosinophilia

BAL : Eosinophilia

Good response to steroid

Warning : Not all points are covered in the notes, especially conceptual explanations. Please use the notes in conjunction with Marrow Edition 4 videos.

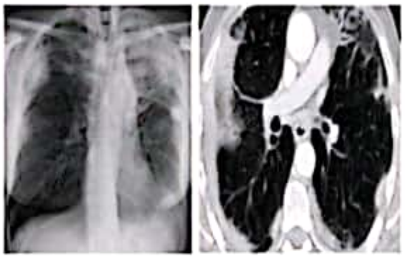
Chronic eosinophilic pneumonia 00:25:44

- F>M , 30-40 y.
- Non smokers
- Asthma/allergic rhinitis
- Subacute to chronic presentation

↓

Low grade fever
Night sweats
Weight loss
+
cough

} R_x – Steroids



- Dyspnoea – progressive
- BAL > 40% eosinophilia

Most important feature – Reverse bat wing/photographic negative of pulmonary edema

Hyper eosinophilic syndrome

- Persisent eosinophilia > 1500 cells/μL with end-organ damage

- End organ damage: myeloproliferative with JAK 2 or PDGFRα mutation
- Involve CVS + CNS + Peripheral neuropathy
- GIT, myocarditis
- Unresponsive to steroids.
- No infiltrates in lung.

Active space

ABPA

Allergic Broncho Pulmonary Aspergillosis

Aspergillus fumigatus (Saprophytic)
Conidia / septate hyphae

↓

patient of long standing cystic fibrosis
or Bronchial asthma (mc)

↓

Colonise in the airways

↓

Type I > Type 3 Hypersensitivity antibodies response

↓

↑ IgE, Eosinophilia, infiltrates, IgG antibody (Precipitins)

↓

Plugging of bronchi with mucus plugs containing hyphae

↓

Inflammation of bronchial wall

↓ Bronchiectasis.

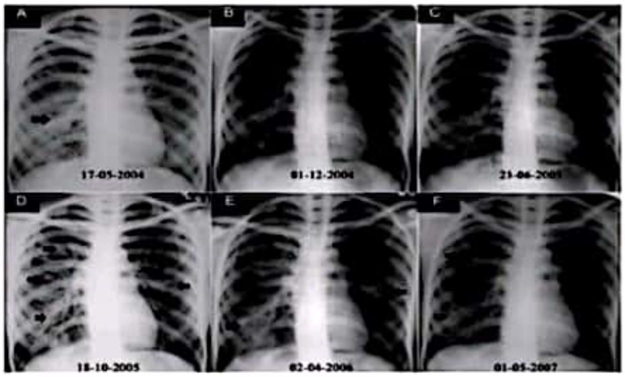
↓ Very rarely can lead to upper lobe fibrosis

- TH$_2$ mediated inflammation with eosinophilia

Pathology Of ABPA

00:05:31

1. Eosinophilic infiltration of lung parenchyma with fleeting radiological Shadows = fleeting opacities



Active space

2. mucus plugging with hyphae leading to atelectasis
3. Bronchial wall damage leading to bronchiectasis

Clinical features

1. Recurrent asthmatic exacerbations
2. Steroid dependent asthma
3. Fever and cough with thick Brownish mucus plugs containing hyphae
4. Crackles / Clubbing seen in < 15% Cases

Proximal cylindrical bronchiectasis / central bronchiectasis

Criteria for ABPA diagnosis

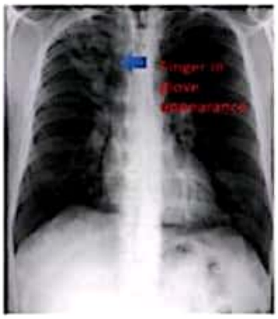
00:09:56

1) Predisposing asthma or CF
2) Obligatory criteria
    a. IgE > 1000 IU / mL
    b. Positive immediate skin test or increased IgE against aspergillus.

3) Supportive (2/3) criteria
    a. Eosinophilia >500
    b. Precipitins or increased IgG antibody to aspergillus
    c. Consistent radiographic opacities

Facts

1. most useful test for diagnosis and follow up IgE levels
2. PFT obstructive (Except stage V – restrictive)
3. Tree in bud sign – Cylindrical and proximal, upper lobe pattern bronchiectasis (rare)
4. Finger in glove appearance – mucoid impaction in dilated bronchi (tooth paste shadows)
5. A/K/A = Tram track Lines.



Management of ABPA

00:16:05

Steroids → 12 weeks

↓ Refractory / relapse

- Anti – IgE antibody = omalizumab
- Itraconazole × 16 weeks
- Airway clearance devices
- Hypertonic saline

- To monitor periodically with ige levels

HYPERSENSITIVITY PNEUMONITIS

Hypersensitivity pneumonitis (HSP)

- A/K/A extrinsic allergic alveolitis
- Organic dust exposure
- Subacute > Acute exposure (Antigen)

↓

Type IV > Type III Hypersensitivity

↓

No IgE / No eosinophilia
Non caseating granulomas

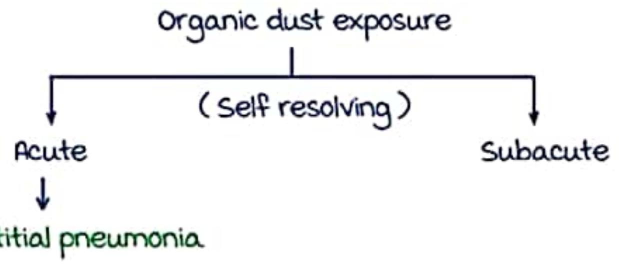
↓

Upper lobe fibrosis
(No risk for bronchiectasis)

- Inflammation in alveolar wall or terminal airway.

Pathophysiology of HSP

00:08:16



Organic dust

Plant Proteins	Exposure
1. Farmers lung (mc)	moldy hay
2. Bagassosis (2nd mc)	moldy sugarcane
3. mushroom workers lung	moldy compost / mushroom
4. Tobacco workers lung	mold on tobacco
5. Compost lung (3rd mc)	Compost
6. wood workers lung	wood pulp
7. Bird fanciers lung	Pigeon / parrots / chicken
8. Chemical workers lung	Polyurethane foams (Isocyanates)

Disease	Antigen
1. Bagassosis, mushroom worker's lung, farmer's lung (mc)	Thermoactinomycetes vulgaris (thermophilic actinomycete)
2. Compost lung, tobacco worker's lung, cheese washers lung	Aspergillus clavatus
3. Hot tube lung, air conditioner's lung	MAC
4. Wood workers lung	Bacillus subtilis
5. Wood trimmers lung	Rhizopus

ABPA V/S HSP

00:16:31

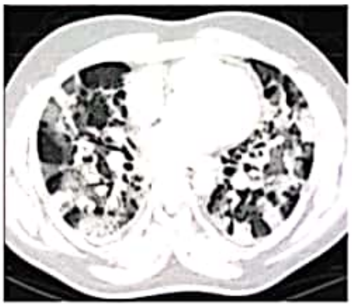
Allergic bronchopulmonary aspergillosis	HSP
1. Bronchial asthma cystic fibrosis	1. Normal
2. Aspergillus fumigatus colonising airway ↓ Type I > Type III	2. Inflammation to organic (Type IV > III) dust Lymphocytic non caseating granuloma
3. Fleeting infiltrates Bronchiectasis Upper lobe fibrosis	3. Diffuse infiltrates no bronchiectasis upper lobe fibrosis
4. Immediate reaction +ve	4. ⊖ve
5. Eosinophil and IgE increased	5. N
6. Precipitins +ve	6. +ve

Active space

CT findings in HSP

00:19:40

IOC – CT



mosaic attenuation
(head cheese pattern)

most HSPs → Fibrosis
Except farmer's lung
↓
Empysematous changes

- Not associated with smoking
- Ground glass opacities with mosaic positive attenuation
- Centrilobular nodules
- Serum precipitins may be positive but it lacks specificity
- BAL : CD4/CD8 increased in sarcoidosis
  CD8/CD4 increased in HSP
- Systemic symptoms ±
- Subacute form is associated with response to steroids

Clinical features

Acute – Fever
Chills
Cough
↑ ESR
Self resolving

Subacute – gradually progressive
Cough & dyspnoea
Fatigability
↓
Chronic – irreversible fibrosis

Other investigations

- PFT restrictive predominantly

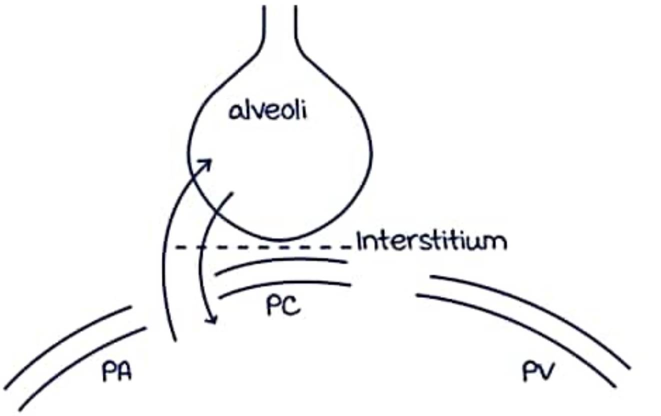
RESPIRATORY FAILURE

Types
1. Oxygenation /diffusion problem
2. Ventilation problem
3. Anaesthesia – post operative lung atelectasis
   medicine – oxygenation + ventilation .
4. Hypoperfusion of respiratory muscles in shock

Type 1 Respiratory failure

00:02:30

- Oxygenation defect



PAO_2 – 100mm Hg

PaO_2 – 97mm Hg

$PACO_2$ = 40mm Hg

$PaCO_2$ = 40mm Hg

Hypoxia $PaO_2 < 60$mm Hg

$SpO_2 < 90\%$

$PACO_2 \downarrow$ – Hypocapnia

(A–a) O_2 gradient : ↑

↓

Hypoxia

Ⓝ to low $PaCO_2$

↑ (A–a) O_2

Causes
1. Interstitial lung disease (most common)
2. Pulmonary edema (ARDS)
3. Pneumonia
4. COPD – Emphysema
5. Acute severe asthma .

Active space

Type 2 Respiratory failure

- Ventilation defect.

Generator : Respiratory Centre : Structural CNS
Drugs, Hypothyroidism
↓
Sedatives, metabolic alkalosis

Pump → Chest wall → Kyphoscoliosis, ankylosing spondylitis
Neuromuscular system — Obesity, Polymyositis, Pleural pathology, MND, myasthenia gravis

Effector
↓
COPD (chronic bronchitis)
$(A\text{-}a)O_2$ Normal
PaO_2 ↓ hypoxia
$PaCO_2$ ↑ hypercapnia

V/Q ratio
I. Dead space ventilation – pulmonary embolism
$V/Q = \infty$
II. Shunt Physiology – collapsed alveoli, $V/Q = 0$

V/Q heterogenity. → pulmonary embolism

Causes of Type 2 respiratory failure

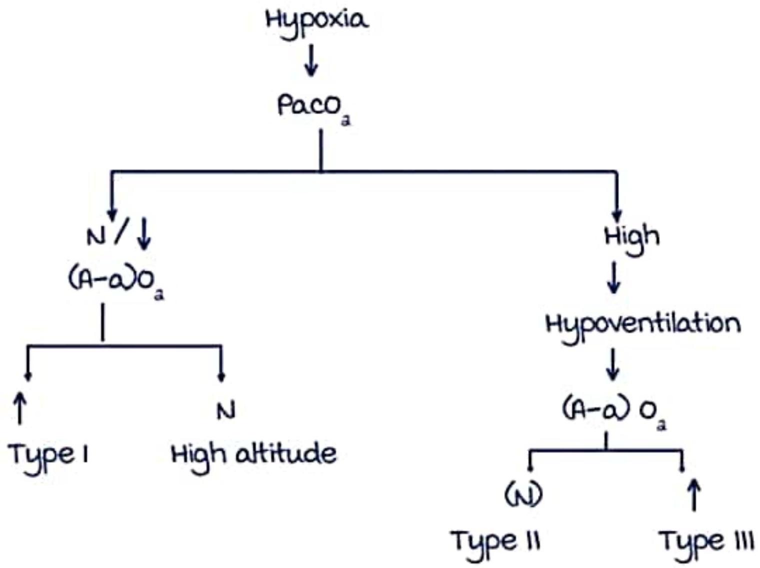
Generator
Pump
Effector
(Pneumothorax
Foreign body
Obesity

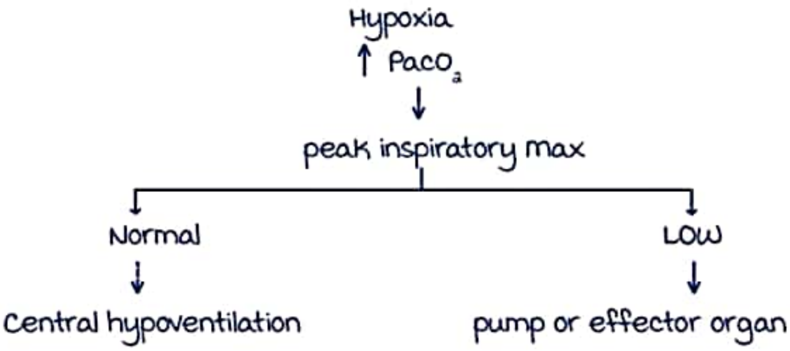
ARDS I → III
ILD I → III
Chronic bronchitis II → III
Emphysema I → III

Type I → Type III
↑ $PaCO_2$
Type 2 → Type III
PaO_2 ↓ $(A\text{-}a)O_2$ ↑
$PaCO_2$ ↑

Approach to hypoxia

00:21:11


Hypoxia
$PaCO_2$
N / ↓
$(A-a)O_2$
↑
Type I
N
High altitude
High
Hypoventilation
$(A-a)O_2$
(N)
Type II
↑
Type III


Hypoxia
↑ $PaCO_2$
peak inspiratory max
Normal
Central hypoventilation
Low
pump or effector organ

V/Q

= 0 Partial pulmonary occlusion
Poor ventilation of normally perfused alveoli
Pneumonia, ARDS, ILD

Heterogenity – pulmonary embolus

= and sign – Large pulmonary embolus

Active space

INTERSTITIAL LUNG DISEASE

- Diffuse parenchymal lung disease involving interstitium, alveoli and vasculature
- Fibrosis mediated by TGF – β > platelet derived growth factor

Classification of ILD

00:02:31

- ILD classified into 2 broad categories
  1. Idiopathic interstitial pneumonia (more common) [IIP]
  2. ILD of Known cause

- IIP
  1. Idiopathic pulmonary fibrosis → Usual interstitial pneumonia (most common) [UIP]
  2. Non-specific interstitial pneumonia (NSIP)
  3. Cryptogenic Organizing pneumonia – COP
  4. Diffuse alveolar damage – Acute interstitial pneumonia
  5. Respiratory bronchiolitis – RB – ILD
  6. Desquamative interstitial pneumonia (DIP)
  7. Lymphocytic interstitial pneumonia (LIP)

- ILD
  1. Occupational – Asbestosis (lower lobe)
     Silicosis (upper lobe)
     Berryliosis (upper lobe)
     Coal worker's pneumoconiosis (upper lobe)

  2. Connective tissue disease : Rheumatoid arthritis (UIP)
     Scleroderma → diffuse
     Polymyositis / Dermatomyositis (NSIP)
     Sjogren's syndrome
     SLE
  3. Sarcoidosis
  4. HSP – Hypersensitivity pneumonitis
  5. Inherited : Tuberous sclerosis
  6. Drugs (NSIP)

- Drugs that cause ILD [NSIP]
  - Amiodarone
  - Nitrofurantoin
  - Bleomycin, Busulfan, cyclophosphamide, methotrexate

- Bromocriptine
- Anti TNF α
- Mitomycin , carmustine

- Causes of upper lobe ILD
  - Silicosis
  - Sarcoidosis
  - CWP
  - Langerhan cell histiocytosis
  - Berryliosis
  - HSP
  - ABPA – Allergic bronchopulmonary aspergillosis
  - Ankylosing spondylitis
  - Tuberculosis .
  - Radiation

Clinical features of ILD

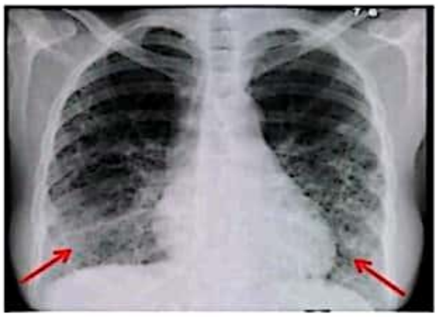
00:13:44

- 2 Cardinal symptoms
  1. Cough : dry, non productive with no diurnal variation . wrongly labelled as bronchitis
  2. Dyspnoea on exertion .

- Other rare symptoms :
  - Hemoptysis
  - Pleuritic pain
  - Wheeze except in cryptogenic organizing pneumonia
    fever + arthralgia except in sarcoidosis

- Signs
  - Clubbing
  - Raynaud's phenomenon → CTD
  - Erythema nodosum → Sarcoid
  - Signs of pulmonary hypertension → grave prognosis
  - Bilateral , bibasal end inspiratory to early expiratory fine crackles not varying with cough . (Velcro crackles)

- X-ray is not diagnostic
  investigation of choice : CT scan

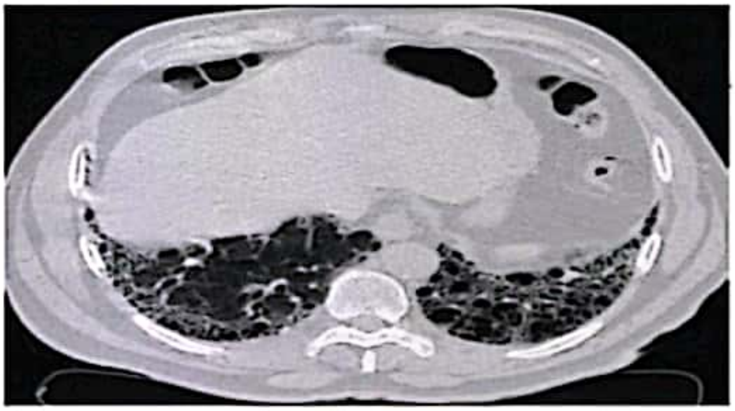


bilateral bibasal subpleural reticular infiltrates

Idiopathic pulmonary fibrosis

00:18:30

- Usual interstitial pneumonia (UIP)
- most common type
- Age : 50 – 70 y
- males > Females
- No effective treatment
- Only one known cause – Rheumatoid arthritis poor prognosis
- Commonly involves lower lobe



Idiopathic pulmonary fibrosis – HRCT. Coarse reticular bibasal fibrosis resembling 'honeycombing'.

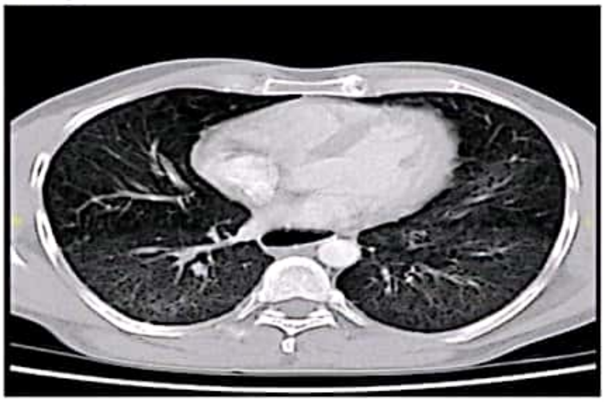
- On CT ,
    - Loss of lung parenchyma
    - Honeycombing pattern
    - Cystic changes
    - Increased septal thickness – Traction bronchiectasis
    - Basal subpleural reticular opacities

- Factors associated with prognosis
    - DLCO
    - Pulmonary hypertension
- HRCT – IOC
- Other investigations
    - BAL and Transbronchial lung biopsy in sarcoidosis
    - Open lung biopsy when diagnosis not definitve

Non specific interstitial pneumonia

00:23:20

- mostly connective tissue disease or drug induced
- Females > males ; in young age group .
- No honeycombing / cystic changes / loss of lung parenchyma on CT .
- Ground glass opacities are seen on CT scan .
- Subacute presentation
- Responds to :
  - Steroid + Azathioprine
    or
    Cyclophosphamide
- Better prognosis than UIP



Other types of ILD

00:26:01

- Smoking related ILD :
  1. DIP : Desquamating interstitial pneumonia
  2. RB – ILD : Respiratory bronchiolitis associated ILD
  3. LCH : Langerhan cell histiocytosis .

- LCH
  - Young male
  - Smoker
  - Nodules and cysts in upper lobe
  - Risk for spontaneous pneumothorax

- DIP
  - Basal ground glass opacities with cysts in a smoker

- RB – ILD
  - Smoker
  - Bronchial wall thickening
  - Centrilobular nodules

Active space

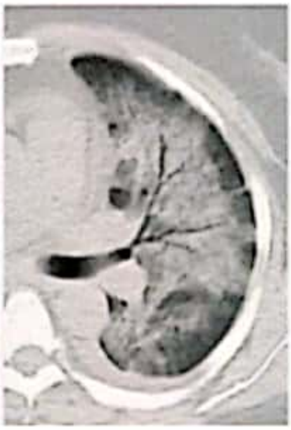
- Pulmonary lymphangioleiomyomatosis
    - Young female
    - Tuberous sclerosis
    - Extensive cyst formation and tissue destruction
    - Pneumothorax or chylous effusion.
    - Angiomyolipoma
    - R_x : mTOR inhibitors : Everolimus

- Lymphocytic interstitial pneumonia (LIP)
    - Associated with HIV & Sjogren's syndrome
    - Classified under NSIP

Cryptogenic organizing pneumonia

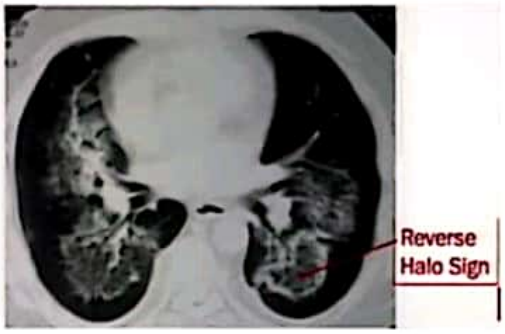
00:31:18

- Previously called BOOP – Bronchiolitis obliterans organizing pneumonia.
- Age = 60 – 70 years
- males = Females
- major secondary cause : Polymyositis
- On PFT, there is restrictive pattern
- Polypoid plugs in bronchiole – masson's bodies
- Cough with productive sputum can be misdiagnosed as TB or community acquired pneumonia
- Steroid responsive
- On CT
    - Consolidation



- Combined consolidation and ground glass opacity

  Reverse halo sign



- Subpleural sparing
- Constrictive bronchiolitis – cliniacal presentation similar to COPD

  Steroid unresponsive

Pulmonary alveolar proteinosis

[illegible]

- Antibody against GM – CSF, reduced clearance of surfactant
- mostly acquired.
  sometimes congenital due to mutation in SP – B gene
- Age : 30 – 50 y
- mostly seen in males
- PAS ⊕ chunky gelatinous sputum
  - Differential : acute silicosis
- On x-ray : Batwing appearance
- Treatment : whole lung lavage

HRCT findings in ILD

1. Reticular and linear shadows (all)
2. Nodular shadows (LCH)
3. Ground glass opacities (NSIP)
4. Consolidations (BOOP)
5. mosaic attenuation and air trapping (HSP)
6. Cysts (UIP / LCH)
7. Traction bronchiectasis (UIP)
8. Honey combing (UIP)

New era in ILD management

- Pirfenidone : anti TGF – β
- Nintedanib : anti PDGF

Acute interstitial pneumonia

00:42:30

- Diffuse alveolar damage
- Fatal acute onset ARDS with bilateral ground glass opacities
- Hamman crunch sound due to mediastinitis
- No treatment
- Extremely high mortality

Obstructive sleep apnoea syndrome (OSAS) 00:00:34

- Obstructive apnoea or hypopnoea during REM sleep resulting in reduction of O_2 saturation.

- Apnoea → Cessation of breathing $\geq$ 10 seconds
  Hypopnoea → Reduction in breathing with 50% or more reduction in amplitude of ventilation or O_2 desaturation by $\geq$ 4% for $\geq$ 10s

- Apnoea hypopnoea index
  - mild OSAS → 5 – 15 episodes / hr
  - moderate OSAS → 15 – 30 episodes /hr
  - severe OSAS → >30 episodes / hr

- Cardinal symptoms → signs of sleep deprivation
  ↓
  Snoring
  +
  → Day time sleeping / fatigue / poor Concentration

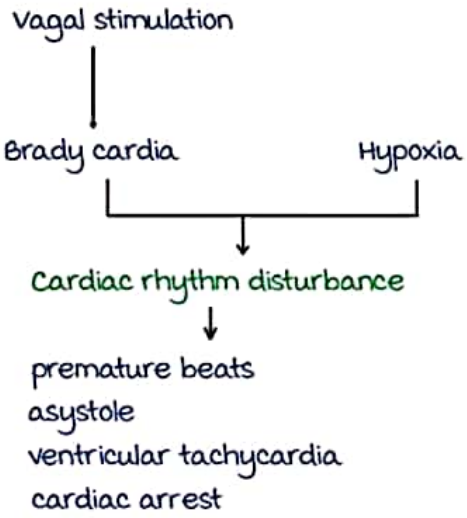
- Risk factors :
  1. males > Females
  2. Obesity : centripetal obesity
  3. Supine sleep position
  4. Smoking
  5. Alcohol
  6. Post menopausal state
  7. Age > 40 years

- Associated with nocturia, unexplained pulmonary hypertension
  Unexplained polycythemia.

- Day time symptoms :
  - ↓ Concentration
  - Cognitive defects
  - Early morning headache
  - Dry throat
  - Excess daytime sleep

- Associated condition :
  - GERD : Gastroesophageal Reflux Disease
  - Hypertension
  - Sexual dysfunction
  - Depression

- High risk for sudden cardiac death


Vagal stimulation
Brady cardia
Hypoxia
Cardiac rhythm disturbance
premature beats
asystole
ventricular tachycardia
cardiac arrest

Warning : Not all points are covered in the notes, especially conceptual explanations. Please use the notes in conjunction with Marrow Edition 4 videos.

- Complication :
  - metabolic syndrome
  - Stroke
  - Congestive cardiac failure
    - Pulmonary hypertension
    - Systemic hypertension.
  - Attention, memory and cognitive dysfunction.

- Diagnosis by Epworth Sleepiness Scale (ESS)

- Investigation of choice : Polysomnography

Central sleep apnoea	Obstructive sleep apnoea
• Cessation of airflow > 10 s with no respiratory effort	• Cessation of airflow >10s with respiratory effort.

- Treatment : CPAP
  (Continous positive airway pressure)

PLEURAL CAVITY

Introduction 00:01:16

- Pleura is lined by mesothelial cells that produce surfactant.
- Pleura – coupling organ between lung and chest wall

- Development
  - Parietal pleura ⟶ somatopleuric mesoderm
  - Visceral pleura ⟶ splanchnopleuric mesoderm

- Pleural lymphatics ⟶ maintains negative intrapleural pressure

- Pleural fluid :
  - Normal : 10 – 30 ml
  - To detect by USG : 50-60ml
  - To detect clinically : 300ml

Light's Criteria 00:05:08

- Pleural effusion can be : Exudative pleural effusion
  Transudative pleural effusion.
- If any one criteria satisfied : Exudative
  no criteria satisfied : Transudative
- If on diuretics, may be falsely classified as exudate

Light's criteria		Exudative
1. $\frac{\text{Pleural fluid protein}}{\text{Serum protein}}$	>	0.5
2. $\frac{\text{Pleural fluid LDH}}{\text{Serum LDH}}$	>	0.6

3. Pleural fluid LDH $2/3^{rd}$ of the upper limit of normal serum LDH

Transudative effusion
- Usually bilateral
- Causes : Congestive cardiac failure (CCF)
  Cirrhosis
  Nephrotic syndrome
  Peritoneal dialysis

Superior vena cava obstruction
myxedema
Urinothorax
Hypoalbuminemia
Budd - chiari syndrome
constrictive pericarditis

- Urinothorax : Transudate with low pH
- High creatinine ammoniacal odour .
- Pulmonary infarction : Exudative or Transudative

Exudative effusions

Causes :

1. TB
2. Pneumonia - Synpneumonic effusion
   parapneumonic effusion
   empyema
3. malignancy
4. Connective tissue disease - SLE Rheumatoid arthritis
5. Acute pancreatitis
6. Occupational Lung disorders - Asbestosis

Causes of drug induced pleural effusion :

- Nitrofurantoin
- Dantrolene
- methysergide
- Bromocriptine

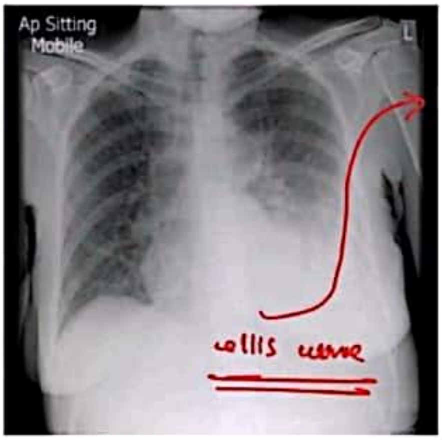
Clinical Features Of Pleural Effusion

00:13:36

- Some examples of clinical scenarios :-
  1) Unilateral effusion with no other clinical findings : short history of cough/ dyspnea / pleuritic pain .
  2) Nephrotic syndrome / CKD / CCF with unilateral effusion .
  3) Pneumonia with persistent fever/
     ↑ WBC counts / effusion (after being on antibiotics for 4-5 days)
  4) SLE with moderate effusion .
- Symptoms :-
  - Fever : when associated with pneumonia , TB .
  - Cough
  - Pleuritic chest pain
  - long duration ; exposure to asbestos
- Signs
  - Tracheal deviation to opposite side .

- Reduced air entry / chest expansion
- Stony dullness
- Decreased vocal fremitus / vocal resonance

- On chest X – ray : Ellis curve



Pneumonia Related Effusions

00:23:22

- Pneumonia related effusions are
  1. simple synpneumonic effusion
  2. complicated parapneumonic effusion
- Empyema = Pus in pleural cavity + complicated parapneumonic effusion
- Empyema or parapneumonic effusion is an absolute indication of ICD (Intercostal drainage) tube thoracostomy and drainage

Simple synpneumonic	complicated parapneumonic
Pleural fluid pH >7.2	<7.2
Pleural fluid gram stain and culture – negative	positive
Pleural fluid LDH <1000	> 1000
Pleural fluid glucose >60g/L	< 60g /dL
USG no pleural thickening	Pleural thickening+ septations+ loculations

- Causes of pleural fluid glucose :
  - < 60g /dl – malignancy empyema
  - < 30 g / dL – Rheumatoid arthritis

Active space

- Causes of pleural effusion with low pH
  1. Empyema / complicated parapneumonic effusion
  2. Rheumatoid arthritis
  3. malignancy (carrries very poor prognosis)

Other Conditions with Pleural Effusion

00:30:54

TB pleural effusion.

- In pleural fluid,
  - AFB stain → 10-20% sensitivity
  - AFB culture → 25-50% sensitivity
  - Gene expert → 45% sensitivity
- Investigation of choice in TB pleural effusion → pleural biopsy (90% sensitivity)

Connective Tissue Disease related pleural effusion.

SLE	Rheumatoid arthritis
Pleuritis ± effusion Small ,bilateral Normal glucose Normal pH	Pleuritis ± effusion moderate , unilateral low glucose low pH

Chylothorax V Pseudochylothorax

Chylothorax	Pseudochylothorax
TG level > 110mg /dl	<50mg /dl
Cholesterol < 200mg / dl	> 200mg / dl
Cholesterol crystals : NO	Yes
Chylomicron : Yes	NO
Acute	Chronic
Trauma > TB > Tumors	Thickening of pleura

Eosinophilic effusion

- Causes :
  1. Parasitic → P. westermani
  2. Hemothorax, Pneumothorax
  3. Pulmonary infarction
  4. Histoplasmosis
  5. Asbestosis
  6. Drugs → Nitrofurantoin

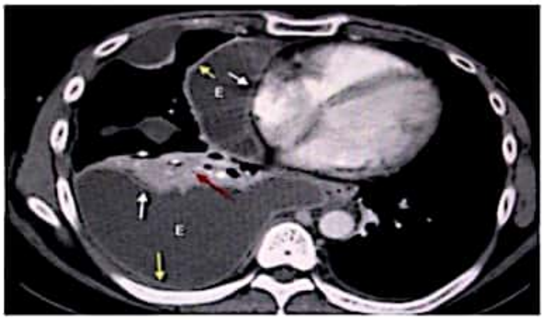
Neoplastic exudative effusions

- most common cause pleural mesothelioma > Adenocarcinoma lung
- metastasis most commonly from Ca breast
- Investigations of choice
    - CT Guided biopsy
    - VAT : Video assisted thoracoscopy
- Cytology yields only in 50%
- Poor prognosis except in Non Hodgkin's lymphoma .

INVESTIGATIONS

00:41:50

- On x- ray :
    - Obliteration of costophrenic angle
    - Air – fluid level in dependent position
    - Ellis curve
    - Empyema appears as a cloudy or opaque area
- On CT : split pleura sign : pus in between thickened parietal and visceral pleura



Active space

COPD

- Chronic airway + alveolar disease leading on to airflow limitation with dynamic compression of airways in COPD

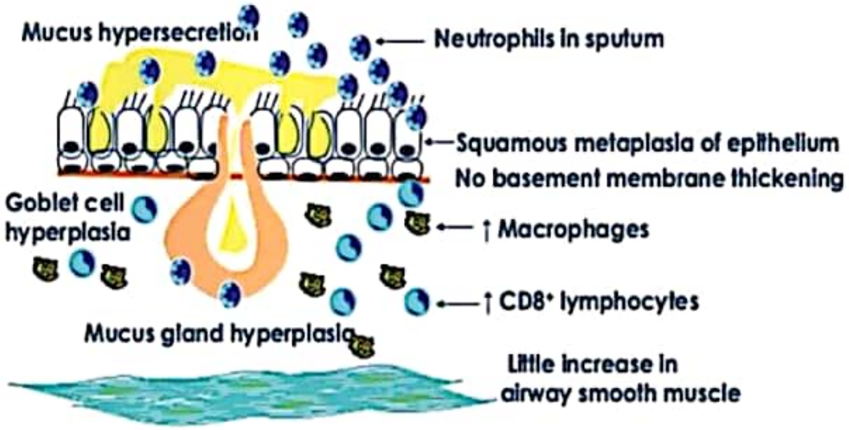
- COPD :
  1) Chronic bronchitis
  2) Emphysema
  3) Small airway disease

Pathology of COPD

00:05:30

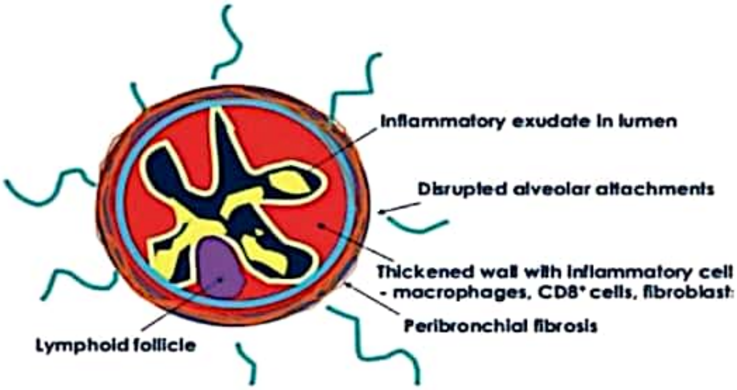
- COPD Comprises pathologic changes in four different compartments of the lungs .
  1) Central airways
  2) Peripheral airways
  3) Lung parenchyma
  4) pulmonary vasculature

Changes in large airways of COPD Patients


Mucus hypersecretion
Neutrophils in sputum
Squamous metaplasia of epithelium
No basement membrane thickening
Goblet cell hyperplasia
↑ Macrophages
↑ CD8⁺ lymphocytes
Mucus gland hyperplasia
Little increase in airway smooth muscle

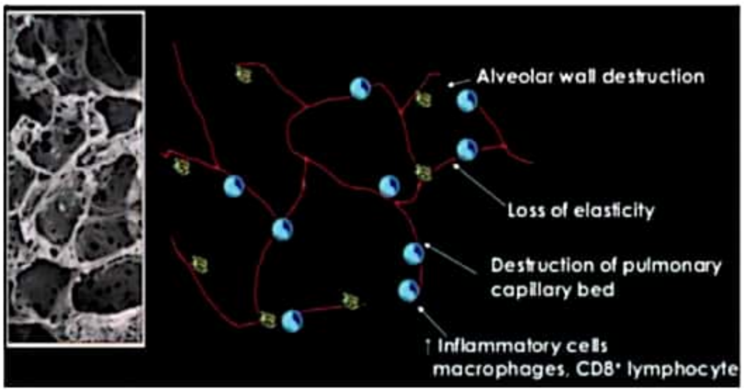
1. Mucus Hypersecretion due to goblet cell hyperplasia
2. Squamous metaplasia
3. Basement membrane thickness remains same
4. Airway smooth muscle – Normal
5. Neutrophils in sputum

Changes in small airways in COPD


Inflammatory exudate in lumen
Disrupted alveolar attachments
Thickened wall with inflammatory cell
- macrophages, CD8$^+$ cells, fibroblast
Peribronchial fibrosis
Lymphoid follicle

1. Dynamic compression of airways
2. Inflammatory exudate in lumen
3. Disrupted alveolar attachments
4. Lymphoid follicles

Changes in lung parenchyma in COPD


Alveolar wall destruction
Loss of elasticity
Destruction of pulmonary
capillary bed
↑ Inflammatory cells
macrophages, CD8$^+$ lymphocyte

1. Alveolar wall destruction
2. Loss of Elasticity
3. Destruction of capillary bed
   Diffusion affected in emphysema-
   Decreased DLCO
   Diffusion normal in chronic bronchitis-
   DLCO- Normal

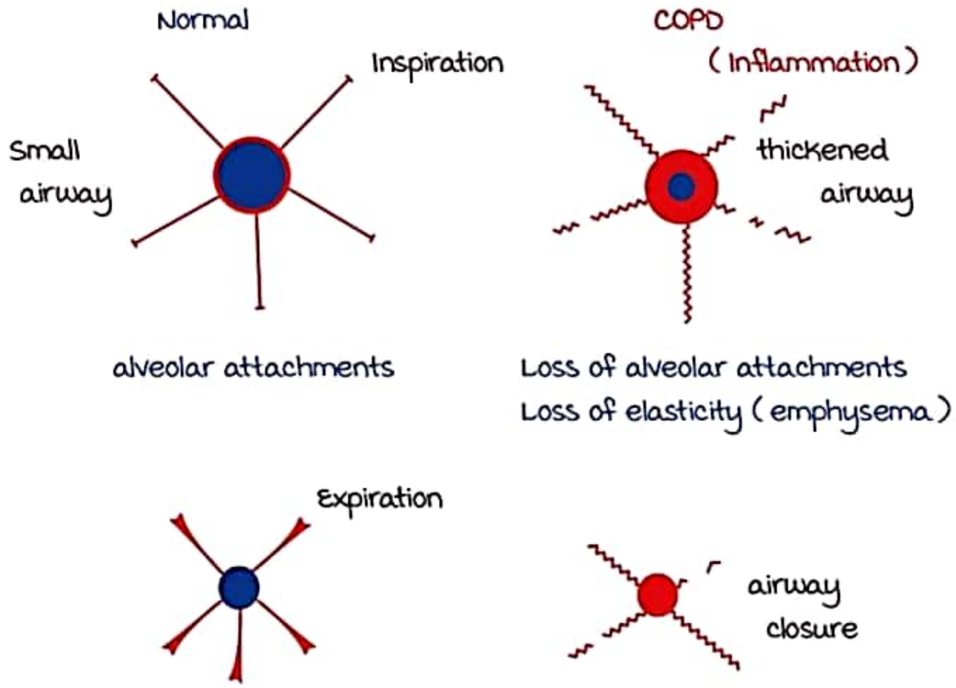
Changes in pulmonary vasculature

Chronic hypoxia
↓
Pulmonary vasoconstriction
↓
Pulmonary hypertension → muscularization, Intimal hyperplasia, Fibrosis, Obliteration
↓
Cor pulmonale → Edema
↓
Death

Large airways- Goblet cells, mucus, squamous metaplasia
Small airways- Dynamic compression+ exudate+ lymphoid follicle
Alveoli- loss of attachments
Vascular- Pulmonary hypertension, cor pulmonale

Air trapping in COPD

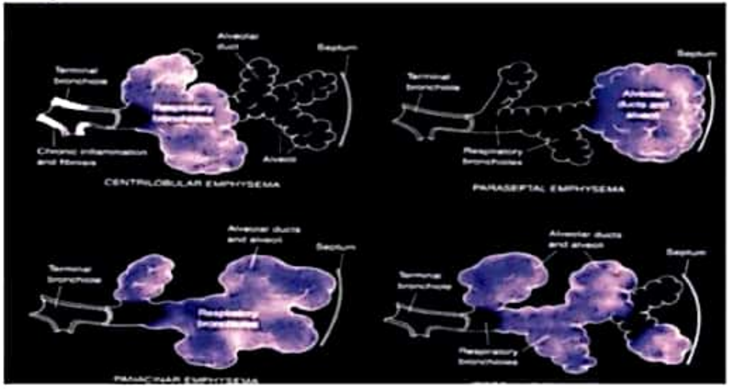
- Dynamic compression ⟶ Air trapping


Normal
Inspiration
Small airway
alveolar attachments
COPD
(Inflammation)
thickened airway
Loss of alveolar attachments
Loss of elasticity (emphysema)
Expiration
airway closure

Types of COPD

00:14:04

- Chronic bronchitis
  - Clinical definition
  - Cough with sputum production for 3 months or more in 2 consecutive years
- Emphysema
  Pathological definition
  - Dilatation of airways distal to terminal bronchiole followed by destruction of the walls of airspaces
  - Types of Emphysema


Terminal bronchiole
Alveolar duct
Septum
Respiratory bronchiole
Chronic inflammation and fibrosis
Alveoli
CENTRILOBULAR EMPHYSEMA
Terminal bronchiole
Septum
Alveolar ducts and alveoli
Respiratory bronchioles
PARASEPTAL EMPHYSEMA
Terminal bronchiole
Alveolar ducts and alveoli
Septum
Respiratory bronchiole
PANACINAR EMPHYSEMA
Terminal bronchiole
Alveolar ducts and alveoli
Septum
Respiratory bronchioles

1. Centrilobular emphysema
   - Centre of acinus involved
   - most common
   - Seen in smokers
   - Predominantly upper lobe

2. Panacinar emphysema
   - Entire acinus involed
   - Seen in young non-smokers
   - Autosomal recessive → α_1 antitrypsin deficiency
   - Protease mediated destruction of lung
   - Pan acinar emphysema + Liver cirrhosis + Vasculitis / Bronchiectasis

   - predominanty lower lobe
   - gene for α_1- Artirypsin → Serpina gene on chr 14

alleles :		
m allele	→	normal , Pimm
S Allele	→	mild deficiency
Z Allele	→	severe deficiency
Null allele	→	no α_1 – antitrypsin

most common : Pizz phenotype

Pimz and Pisz → α_1 antitrypsin deficiency

3. Paraseptal emphysema
   - Seen in young males
   - Increased risk for Spontaneous pneumothorax

Chronic bronchitis and emphysema

00:23:00

	Chromic bronchitis	Emphysema
Age	40 – 50 years	50 – 70 years common in smokers
Symptoms	Cough with sputum	
Definition	clinical, blue bloate	Dyspnea predominantly
Sign		Pathological, pink puffer Cachectic
Pathology	Goblet cell hyperplasia+mucus hyperplasia-	-Loss of elastic recoil pressure -Hyperinflated lung
PFT	Repeated infections- CO_2 retention+	-Airtrapping -Increased work of breathing
Chest x ray	hypoxia- type-II	
Respiratory failure	repiratory failure. Due to Cyanosis Known as Blue bloaters	-Cough minimal -No evidence of right

	Elastic recoil- normal, no evidence of hyperinflation Pulmonary hypertension- Right sided heart failure- cor pulmonale Dyspneoa mild DLCO - Normal TLC normal DLCO normal normal Type II	-CO_2 washout -$PaCO_2$ generally normal to low Hoover sign Hyper-resonance Pursed lip TLC, RV high DLCO low AP diameter increased Type I

Hoover sign : Inward movement of lower ribcage during inspiration due to increased respiratory effort.

- Risks factors for COPD
  - Smoking : strongest risk factor for bronchitis and emphysema (emphysema > bronchitis)
  - Environmental exposure : fuel exposure
    air pollution

Classification of COPD 00:33:10

- based on GOLD 2019 guidelines
- In COPD, $\frac{FEV_1}{FVC} < 70\%$
- Post bronchodilator FEV_1 is measured ;

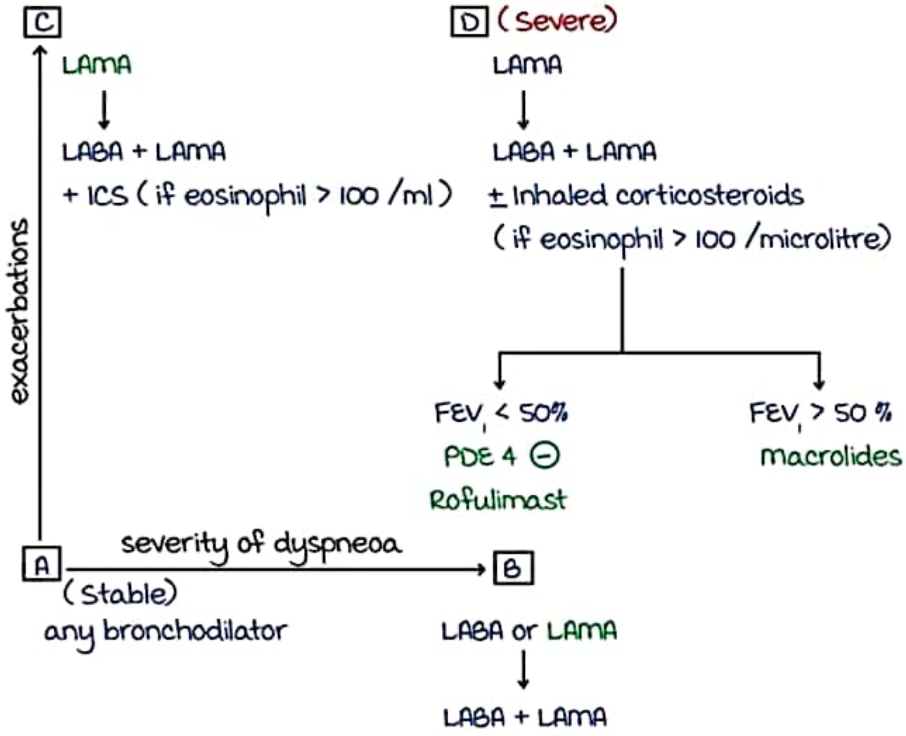
FEV_1 > 80 %	mild	GOLD 1
50–80 %	moderate	GOLD 2
30–50 %	Severe	GOLD 3
< 30 %	Very severe	GOLD 4

Management of COPD 00:35:34

- According to GOLD 2019 Update
  - ICS (inhaled corticosteroids) are not first line due to increased risk of infections
  - Patients are divided into 4 groups based on severity of dyspnea (B) and, number of exacerbations (C)

(> 2 or 1 requiring hospitalisation)

- LAMA – Long acting muscarinic antagonist – Tiotropium
- LABA – Long acting B_2 agonist – fometerol
- PDE_4 inhibitor – Phosphodiesterase – n inhibitor → Rofulimast


C
LAMA
LABA + LAMA
+ ICS (if eosinophil > 100 /ml)
D (Severe)
LAMA
LABA + LAMA
± Inhaled corticosteroids
(if eosinophil > 100 /microlitre)
FEV_1 < 50%
PDE 4 ⊖
Rofulimast
FEV_1 > 50 %
macrolides
exacerbations
A
(Stable)
any bronchodilator
severity of dyspneoa
B
LABA or LAMA
LABA + LAMA

- BODE Index
  - BMI
  - O– Obstructive ventilatory defect
  - Dyspneoa severity
  - Exercise capacity

- To reverse structural abnormalities
  - Smoking cessation : foundation of treatment
  - LTOT: Long term O_2 therapy (16–18 hrs /day)

- In highly localized emphysema : Long volume reduction surgery
  contraindications are:
  - Severe heart failure
  - FEV_1 < 20 %

Bronchial asthma 00:00:51

- Based on 2019 GINA – Global initiative for Asthma
  Asthma pathogenesis :
  - Airway hyper responsiveness
  - Associated with inflammation → various triggers or unknown etiology
  - Variable airflow obstruction → Obstructive airway disease.
- Gene : Chromosome 5q polymorphism
- Symptom : Dyspnea
  Wheeze
  Chest tightness

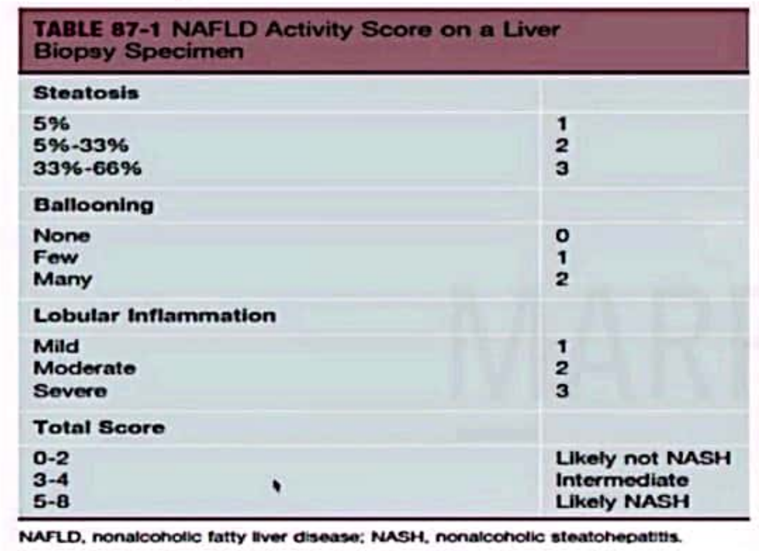


TABLE 87-1 NAFLD Activity Score on a Liver Biopsy Specimen

Steatosis	
5%	1
5%-33%	2
33%-66%	3
Ballooning	
None	0
Few	1
Many	2
Lobular Inflammation	
Mild	1
Moderate	2
Severe	3
Total Score	
0-2	Likely not NASH
3-4	Intermediate
5-8	Likely NASH

NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

Triggers 00:04:57

① URI
(2) Hyperventilation
(3) Aspirin, beta blockers
(4) Sulfur dioxide
(5) paint fumes

Risk factors :
① Obesity
(2) Increased maternal age
(3) 5q polymorphism
(4) maternal Vitamin D deficiency
(5) Hygiene Hypothesis

Active space

At birth → TH_2 Phenotype

Normally, exposure to many Outdoor antigens
↓
TH_1 phenotype
↓
Asthma disappears

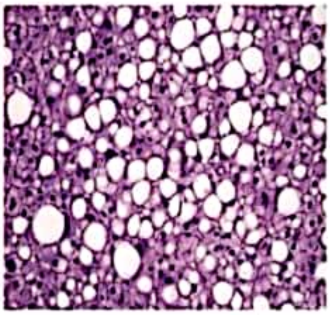
No exposure to allergens
↓
Persistence of TH_2 phenotype
↓
Asthma persists

Eosinophils in Asthma :

- TH_2 mediated
- Release : IL-5 → Eotaxin
  ↓
  Granular proteins
  ↓
  (1) MBP → major basic protein
  (2) EDN → Eosinophilic derived neurotoxin
  (3) ECP → Eosinophil cationic protein
  (4) EPO → Eosinophilic peroxidase

Micropathological changes in asthma

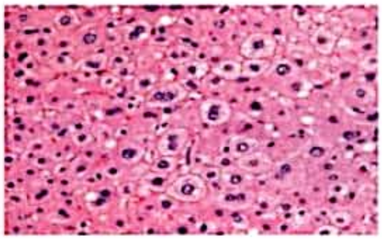
00:10:09



- Mucus plugs
- Curschmann Spirals → Basophilic plug from lower airways
- Charcot-Leyden crystals
  → Galectin - 10 protein
- Eosinophilic infiltration
- Patchy epithelial necrosis
- Submucosal gland hyperplasia
- Hypertrophy of smooth muscles

Note :

- 15% of children and 12% adults are affected world wide.
- In children : Boys > Girls
  Adults : Males = Females
  > 50 years : Females > Males



Extrinsic asthma	Intrinsic asthma
[Atopic] childhood onset	Adult onset
Type I Hypersensitivity	Negative skin test
↑ IgE levels	Normal IgE levels
Associated with : - Allergic Rhinitis - Dermatitis	Super antigen : Staph aureus enterotoxin
mc allergen - Dermatophagoides (house dust mites)	Samter's triad - Intrinsic asthma - Aspirin intake - Nasal polyps
Good prognosis	Bad prognosis

- Common features :
  - → Sputum findings
  - → Pathology .

Definition :

- Based on 2019 GINA guidelines :
- FEV_1 increased by > 200 ml and > 12% of the baseline value (or in children, increase by > 12% of the predicted value) after inhaling a bronchodilator.

  ↓

  " Bronchodilator reversibility "
- Variability in PEFR > 10% (in children > 13%)
- FEV_1 increase more than 12% and 200 ml from baseline (in children, by > 12% of the predicted value) after 4 weeks of anti inflammatory treatment.

→ Bronchial asthma → Type I Respiratory failure
→ ↑ DLCO

Classification of asthma

00:18:13

[I] Intermittent asthma

[II] mild persistent asthma :

- Symptoms : Day time → 2 - 6 per week
  Night time → ≥ 2 per month
- Not affecting daily activities.

[III] moderate persistent asthma :

- Symptoms : Day time → Daily
  Night time → ≥ 1 weekly
- Affects daily activities.

[IV] Severe persistent asthma :

- Continuous day time symptoms with most nights symptomatic
- Affects daily activities.

[V] Asthma with impending respiratory failure.

Acute severe asthma	Asthma with impending Respiratory failure
• Dyspnoeic, speaks in words.	• mute patient
• Agitated patient	• Silent / confused
• Loud wheeze throughout respiration	• Silent chest
• Respiratory rate : 30/min	• Respiratory rate : 30/min
• Peak Expiratory flow <40 ml/min	• PEF < 25 ml/min
• Accessory muscles used	• Paradoxical breathing
• Heart rate > 120 Tachycardia	• Relative bradycardia
• Pulsus paradoxus ⊕ – PEFR < 40ml/min	• Absent (respiratory muscle fatigue), PEFR < 25ml/min

- PaO_2 Saturation → < 60 mmHg (< 90%)
  $PaCO_2$ → < 40 mmHg

Spirometry findings :

① Peak Expiratory Flow Rate → PEFR

(2) maximum mid Expiratory Flow Rate → MMEFR

	FEV_1	PEFR	MMEFR
mild asthma	70 – 80%	normal	50 – 80%
moderate asthma	50 – 70%	60 – 80%	30 – 50%
Severe asthma	< 50%	< 60%	< 30%

Management of asthma

00:29:34

- Based on 2019 GINA strategy :

① Short acting β – 2 agonist (SABA) alone → Not recommended

↓

Regular / frequent use → increase risk of exacerbations

(2) Adults / adolescents with asthma

↓

management : Daily low dose Inhaled corticosteroids

↓

Reduce risk of serious exacerbations

Management :

- Intermittent asthma :

  Low dose Inhaled Cortico Steroids (ICS) + Formoterol (preferred)

  ↓

  1. Beclomethasone 200 - 600 mg
  2. Budesonide 200 - 400 mg
  3. Fluticasone 100 - 250 mg
- Duration of Short acting β_2 agonist → 3 - 6 hours
- 24 hours acting β_2 agonist → Indacaterol
- Mild persistent asthma → Daily low dose ICS
- Moderate persistent asthma →

  Daily low dose ICS + Long acting β_2 agonist (LABA)
- Severe persistent asthma →

  Daily medium dose ICS + LABA

  ↓ no response

  High dose ICS + LABA

  → Anti IgE → Omalizumab (Subcutaneous once in 3 months)

  → Anti IL-5 → Mepolizumab

  → Anti IL-4 → Reslizumab

Note :

- Assess airway hyper responsiveness → MCT

  [methacholine challenge test]
- IgE levels → RAST [radio allergosorbent test]
- Non invasive test to assess airway inflammation

  ↓

  Fractional exhalation of Nitric oxide [FeNO]

Brittle asthma and exercise induced asthma

00:39:40

Brittle asthma :

- Recurrent asthma despite adequate treatment
- 2 types

Type 1	Type 2
- Recurrent asthma with wide peak flow variation	- Sudden severe exacerbations on a background of controlled asthma
- Does not touch baseline	- Baseline touched
- Management : Oral corticosteroids	- Management : Adrenaline (Subcutaneous)

Exercise induced asthma :

- Management : SABA (Short Acting β_2 agonist) prevention : Budesonide + Formoterol

Management of acute severe asthma

00:42:27

- Nasal oxygen (maintain SPO_2 > 90 – 95)
- Albuterol 2.5 – 5 mg ⊕ ipratropium (500 mg)

  ↓

  3 doses every 20 mins

  or

  4 – 8 puffs by MDI every 20 minutes

- IV Hydro cortisone 100 mg

  ↓ no response

  IV $mgSO_4$ (2 gm over 20 minutes)

  ↓ no response

  Non invasive positive pressure ventilation

  ↓

  Intubation

Steroid resistant asthma

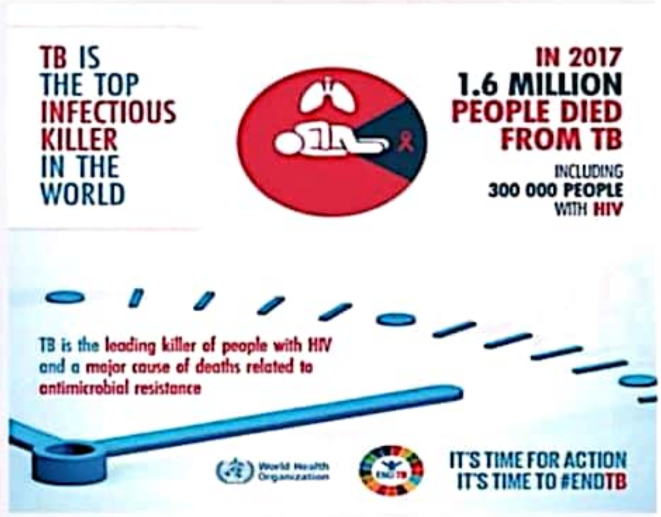
- Alternative splicing of GR-beta [Glucocorticoid receptor]
- Abnormal histone acetylase pattern
- HAC / IL – 10 polymorphism

TUBERCULOSIS - INTRODUCTION AND MICROBIOLOGY

Introduction

World Tuberculosis (TB) day - 24th march
Robert Koch -identified mycobacterium tuberculosis in
24th march, 1882

Tuberculosis : statistics and introduction 00:04:15



TB IS THE TOP INFECTIOUS KILLER IN THE WORLD

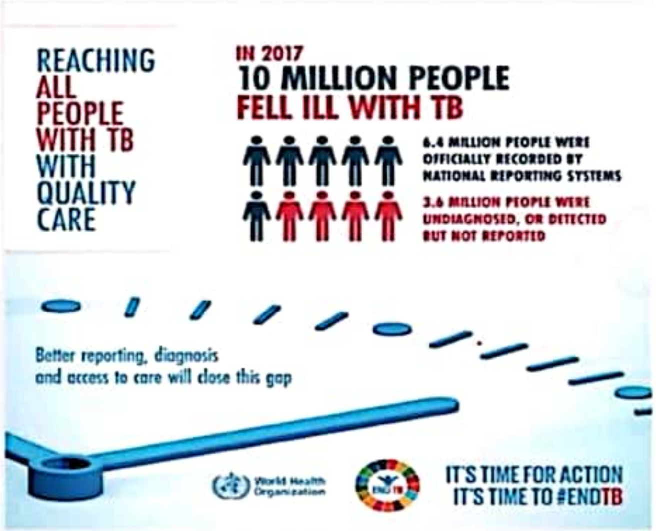
IN 2017 1.6 MILLION PEOPLE DIED FROM TB

INCLUDING 300 000 PEOPLE WITH HIV

TB is the leading killer of people with HIV and a major cause of deaths related to antimicrobial resistance

World Health Organization

IT'S TIME FOR ACTION
IT'S TIME TO #ENDTB



REACHING ALL PEOPLE WITH TB WITH QUALITY CARE

IN 2017 10 MILLION PEOPLE FELL ILL WITH TB

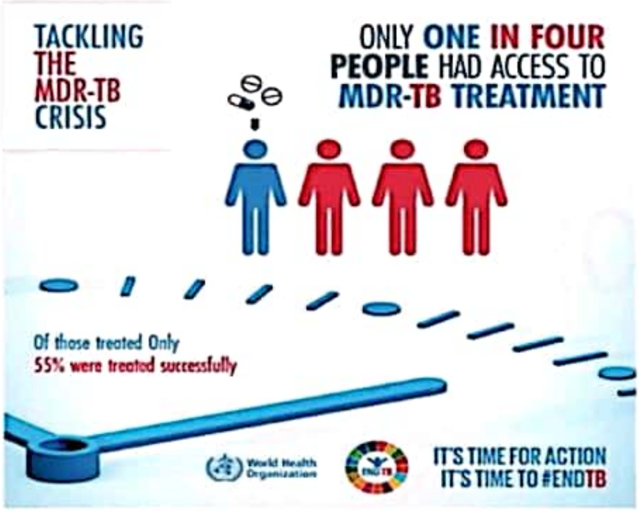
6.4 MILLION PEOPLE WERE OFFICIALLY RECORDED BY NATIONAL REPORTING SYSTEMS

3.6 MILLION PEOPLE WERE UNDIAGNOSED, OR DETECTED BUT NOT REPORTED

Better reporting, diagnosis and access to care will close this gap

World Health Organization

IT'S TIME FOR ACTION
IT'S TIME TO #ENDTB


TACKLING THE MDR-TB CRISIS
ONLY ONE IN FOUR PEOPLE HAD ACCESS TO MDR-TB TREATMENT
Of those treated Only 55% were treated successfully
World Health Organization
IT'S TIME FOR ACTION
IT'S TIME TO #ENDTB

Tuberculosis

- Classification of gram positve rods
  - Spore forming
    - Bacillus
    - Clostridium
  - Non spore forming
    - Corynebacterium
    - Lactobacillus
    - mycobacterium
- Pathogenic species of mycobacterium
  - m. ulcerans → Causes Skin Ulcers
  - m . leprae → Causes leprosy
  - m . tuberculosis → Causes tuberculosis

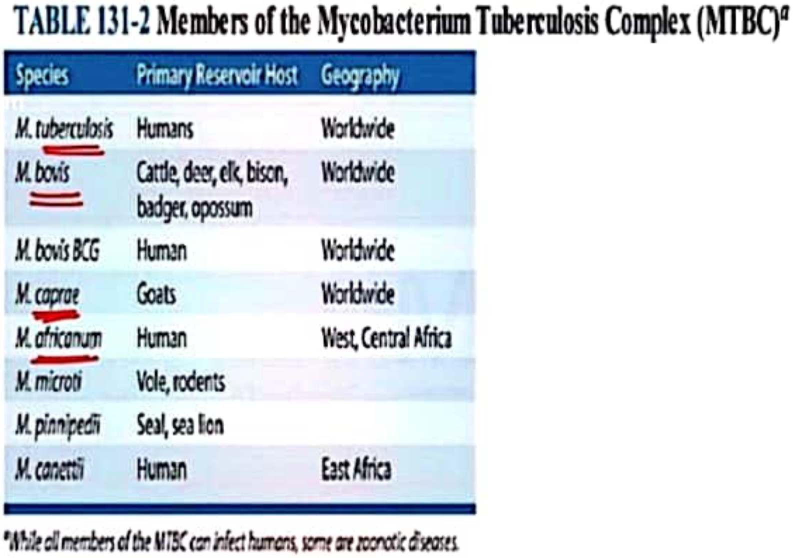


TABLE 131-2 Members of the Mycobacterium Tuberculosis Complex (MTBC)[a]

Species	Primary Reservoir Host	Geography
M. tuberculosis	Humans	Worldwide
M. bovis	Cattle, deer, elk, bison, badger, opossum	Worldwide
M. bovis BCG	Human	Worldwide
M. caprae	Goats	Worldwide
M. africanum	Human	West, Central Africa
M. microti	Vole, rodents	
M. pinnipedii	Seal, sea lion	
M. canettii	Human	East Africa

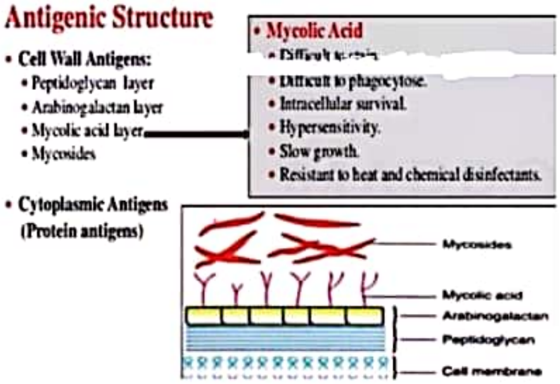
[a]While all members of the MTBC can infect humans, some are zoonotic diseases.

M. tuberculosis : characteristics 00:10:54

- mycobacterium – Gram neutral (not strongly gram positive)
- Obligate aerobe
- Non-spore forming
- Non motile
- Facultative intracellular
- 0.2 to 0.6 × 2 – 4 µm
- Slow generation time – 15-20hrs (may contribute to virulence)
- Acid fast bacilli.

Warning: Not all points are covered in the notes, especially conceptual explanations. Please use the notes in conjunction with marrow Edition 4 videos.

M. tuberculosis structure 00:13:25



Antigenic Structure

- **Cell Wall Antigens:**
  - Peptidoglycan layer
  - Arabinogalactan layer
  - Mycolic acid layer
  - Mycosides
- **Cytoplasmic Antigens (Protein antigens)**

- **Mycolic Acid**
  - Difficult to stain
  - Difficult to phagocytose.
  - Intracellular survival.
  - Hypersensitivity.
  - Slow growth.
  - Resistant to heat and chemical disinfectants.

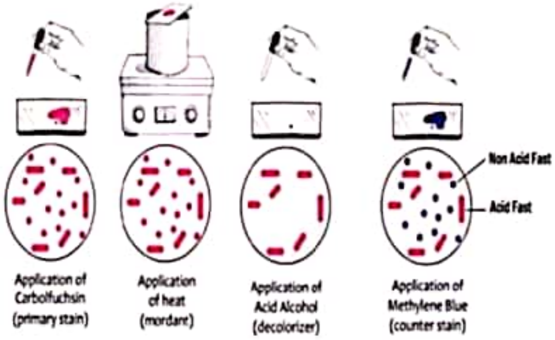
- Cell wall antigens – Peptidoglycan layer
  Arabinogalactan layer
  mycolic acid layer
  mycosides

mycolic acid layer is the reason for

- Difficulty in staining
- Resistance to chemical disinfection
- Acid fastness
- Difficult to phagocytose
- Slow generation time
- Intracellular survival

Active space

Steps in staining


Non Acid Fast
Acid Fast
Application of Carbolfuchsin (primary stain)
Application of heat (mordant)
Application of Acid Alcohol (decolorizer)
Application of Methylene Blue (counter stain)

Instead of methylene blue, malachite green can be used

Biochemical tests and staining methods 00:18:31

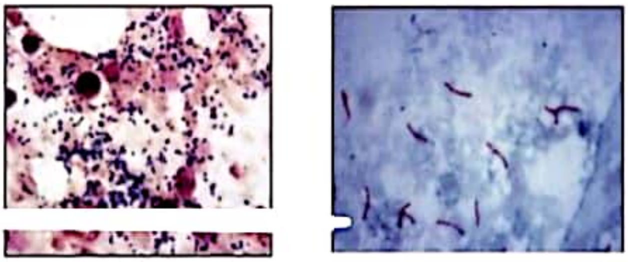
Biochemical tests for m. tuberculosis

1) Nitrate test positive
2) Niacin reduction positive
3) Urease positive

- Catalase positive for – non tuberculous mycobacterium

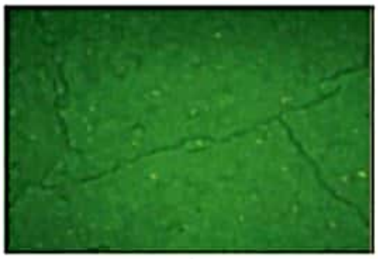
Gram staining

- Ziehl – neelsen staining – m. tuberculosis appearing as bright red bacilli (rods)



Fluorescent stains

- Good for labs with high workload
- Auramine – o – bright yellow organism
- Auramine -o-Rhodamine -B- yellow orange organism



Auramine O

Auramine-Rhodamine

Cultural characteristics of M. tuberculosis

00:21:21

- Aerobe - due to presence of high Guanine + cytosine content
- Growth stimulated by - 5-10 % CO_2
- Conventional solid media - Lowenstein - Jensen medium (L-J)
- The colonies take upto 6-8 weeks for growth

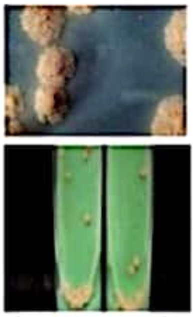
↓

Grows at 31°C

pH - 6.4- 7

↓

Rough, tough & buff colonies



Solid medium

medium with Egg - L-J medium, Dorsets egg

LJ medium constituents - Hens egg, glycerol, mineral salt, asparagine, malachite green

medium with blood - Tarshis medium

medium with potato - Pawlowsky medium

Liquid medium - mycobacterium

1) middle brooks
2) Sula
3) Sauton
4) Beck's
5) Dubos

- Inhaled droplet nuclei < 5 μm is the most infective

- Infective dose - $> 10^4$ organisms / ml of sputum

Active space

- Deposits in highest perfusion and ventilation area of the lung

  ↓

  especially in Lower and middle part of lung

- most infective stage – Post primary TB

  Secondary TB

Pulmonary tuberculosis - pathogenesis 00:00:09

1. Inhalation of organism

⇓

CMI [Cell mediated Immunity]

Immune Response Effective

⇓

Asymptomatic
1° tuberculosis (TB)

- about 95 % cases
- Latent TB
- Tuberculin skin test ⊕
- ↑ risk of reactivation

Immune response - defective

⇓

Symptomatic 1° TB

- only 5 % cases

2. Cell mediated immunity - initiation & consequences

Pulmonary alveolar macrophage

⇓

Present the organism to a T-cell

⇓

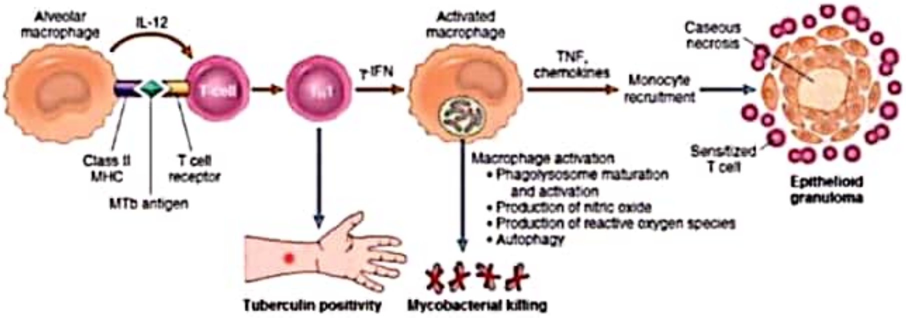
TH1 response

⇓ Interferon - γ released

Phagolysosome - maturation

⇓

Epitheloid granuloma with central caseous necrosis


Alveolar macrophage
IL-12
T cell
Class II MHC
MTb antigen
T cell receptor
TH1
γ-IFN
Activated macrophage
TNF, chemokines
Monocyte recruitment
Caseous necrosis
Sensitized T cell
Epithelioid granuloma
Macrophage activation
• Phagolysosome maturation and activation
• Production of nitric oxide
• Production of reactive oxygen species
• Autophagy
Tuberculin positivity
Mycobacterial killing

3. Antigens of the organism

a. Mannose Lipoarabinomannan.

- An antigen of arabinogalactan layer
- Helps the organism
- to survive inside the phagosome

- to bind to macrophages

b. ESAT – 6

- Induces the secretion of mmp – 9 [matrix metalloproteinase – 9]
- mmp – 9 ⇒ responsible for granuloma formation .

Note

Acid fastness is due to mycolic acid ⇒ a long chain cross linked fatty acid on cell wall .

Primary TB - symptomatic & asymptomatic

00:09:10

1. Asymptomatic 1°TB .
   - mostly seen in children

a. Ghon Complex
   - typical of 1°TB in a child
   - X – ray ⇒ • small foci of consolidation in the lung
     - seen in lower lobe mostly [1°TB]
   - Ghon's Focus ⇒ Caseous granuloma
   - Ghon's complex or Ranke's complex ⇒ Ghon's Focus + Draining lymphnodes [LN]

b. Healing process
   - Granuloma ⇒ heals by fibrosis
   - Lymph Nodes ⇒ heal by calcification

c. Cavitation Reaction
   - does not occur in asymptomatic 1° TB .

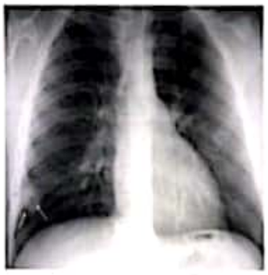
d. Reaction in asymptomatic 1° TB
   - Especially in children

i) mild pleurisy

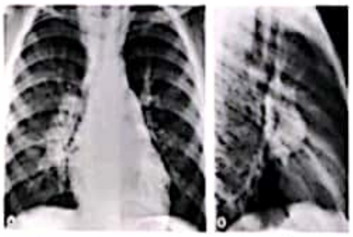
ii) Erythema nodosum

iii) Phlyctenular conjunctivitis

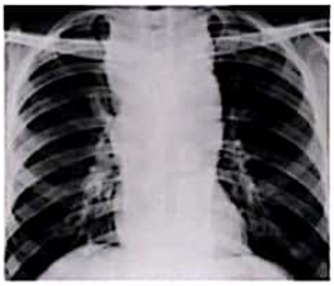
e. Lymphadenopathy
- Hilar > Right Paratracheal
- 2/3rd unilateral
- associated with Ghon's focus
- in children, it may be the only manifestation of 1° TB
- heal by calcification



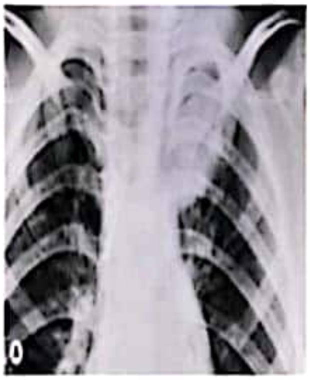
Ghon's focus in lower lobe



Right hilar adenopathy but no pulmonary consolidation

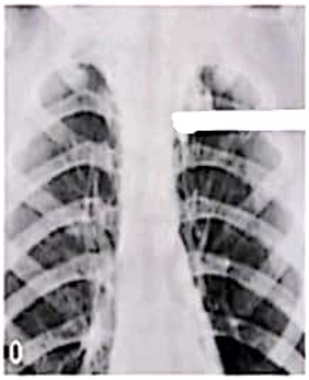


massive mediastinal adenopathy and right hilar adenopathy



↓

Left apical consolidation

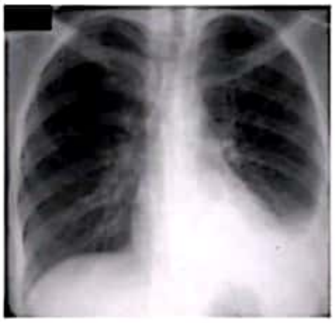


↓

1 yr later ⇒ Apical calcification

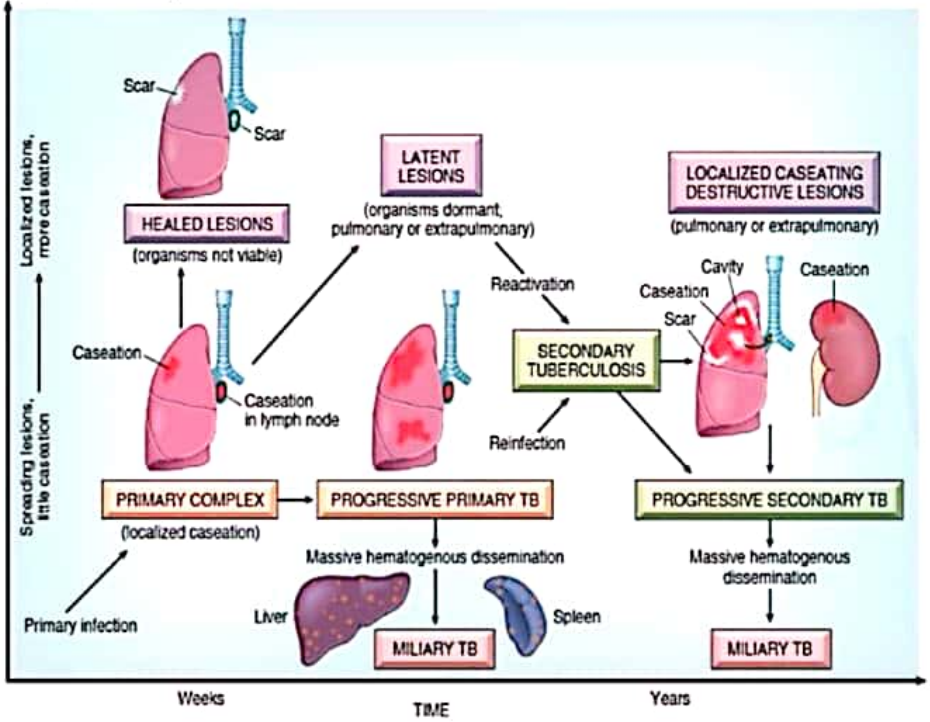
a. Symptomatic 1°TB
- Seen only in 5 % cases (less frequent)
- also known as progressive 1°TB
- seen in • children
  - • elderly
  - • immunocompromised
- Usually involves → middle and lower lung zones
- Symptomatic 1°TB ⇒ Cavitating pneumonia [liquefactive Caseous Necrosis] of middle and lower lobe
  +
  Pleural effusion
  +
  Collapse due to compression of bronchi
- Pleural effusion ⇒ • Usually unilateral
  - • Common in adult [40 %]
  - • more Common with asymptomatic than symptomatic

Note
- Consolidation
  - • Exudates filled in the alveoli
  - • Intact alveoli
  - • Heterogenous opacity



Active space

Course of TB


Scar
Scar
HEALED LESIONS
(organisms not viable)
LATENT LESIONS
(organisms dormant, pulmonary or extrapulmonary)
LOCALIZED CASEATING DESTRUCTIVE LESIONS
(pulmonary or extrapulmonary)
Localized lesions, more caseation
Spreading lesions, little caseation
Caseation
Caseation in lymph node
Reactivation
SECONDARY TUBERCULOSIS
Reinfection
Cavity
Caseation
Scar
Caseation
PRIMARY COMPLEX
(localized caseation)
PROGRESSIVE PRIMARY TB
PROGRESSIVE SECONDARY TB
Massive hematogenous dissemination
Massive hematogenous dissemination
Primary infection
Liver
MILIARY TB
Spleen
MILIARY TB
Weeks
TIME
Years

Secondary tuberculosis

00:20:27

- Also known as (aka) post - primary TB

1. mechanism of secondary TB

Reactivation	Reinfection
- Reactivation of latent TB infection	- more common in India
- Risk of reactivation depends on immune status [↓ immunity → ↑ risk]	- Also known as symptomatic TB
- more common cause overall	- Previously sensitised host

2. Site of involvement in secondary TB

Apical segment of right upper lobe > posterior segment of right upper lobe > superior segment of left lower lobe

[Reason – ventilation – perfusion ratio is ↑ in upper lobe
⇓
↑ growth of organisms]

3. Presentation in 2°TB
- ↑ tissue necrosis and Cavitation
- Hallmark feature → Cavitation [cavitating pneumonia]
- Pneumonia → consolidation → cavitation
  [Air-fluid level due to 2°infection]
- Cough with hemoptysis
- Hemoptysis
  - mild ⇓ Pulmonary artery involvement
  - Severe ⇓ Bronchial artery [systemic artery] involvement
- Amphoric breath sound
  - seen in supeficial / small cavities connected to a patent bronchus
  - A low pitched bronchial breath sound with high pitched metallic overtone [india]

4. Evaluation of TB [India] – Indications

i) Low grade fever + drenching night sweat + evening rise in temperature

ii) Cough with hemoptysis × 2 weeks

iii) 20 % cases with PUO [Pyrexia of Unknown Origin] ⇒ TB

IV) malaise / fatigue / weight loss

v) TB may be the
- sole differential diagnosis (D/D) in a non-resolving pneumonia
- main D/D in lobar pneumonia

vi) Anaemia of chronic disease [usually → Normocytic Normochromic]

vii) Pancytopenia

viii) Hyponatremia

Secondary TB - lesions, radiological findings & complications

00:32:14

1. Foci / Complexes / Lesions

a. Simon focus – The only foci to be seen in 1°TB
- nodule → at the apex

b. Puhl's focus
- seen in 2° TB
- supraclavicular foci

c. Assmann's focus
  - seen in 2° TB
  - infraclavicular foci

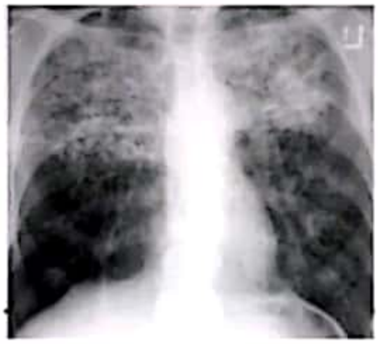
d. Rich's focus
  - seen in 2° TB
  - Brain parenchyma

e. Simmond's focus
  - seen in 2° TB
  - Liver

f. Wigard's focus
  - seen in 2° TB
  - Pulmonary vein → intimal layer

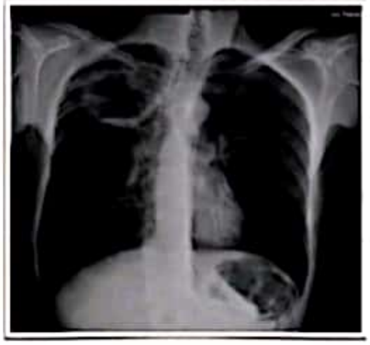
2. Secondary TB → Radiological Finding

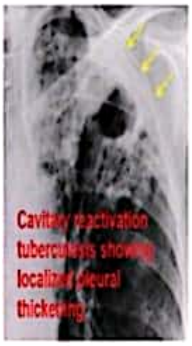
a. Consolidation

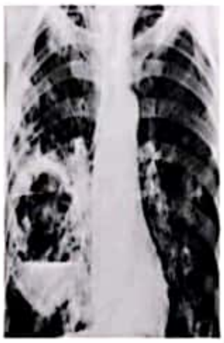


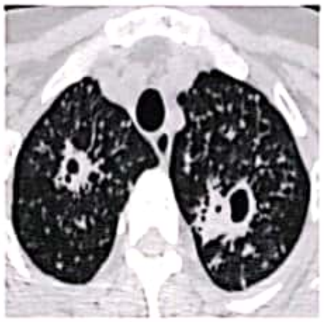
- Focal / Patchy heterogenous consolidation involving the apico - posterior segment of upper lobe and superior segment of lower lobe

b. Cavitary lesions




Cavitary reactivation tuberculosis showing localized pleural thickening

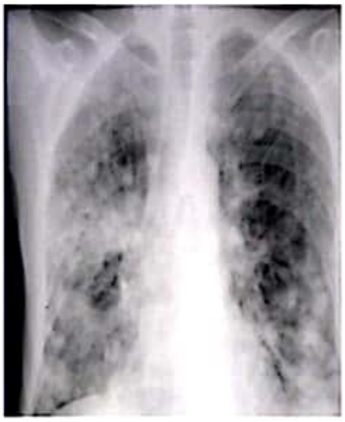




Active space

- Characteristic feature of post - primary / 2°TB
- Cavitation ⇒ implies high infectivity
- cavity size ⇒ Ranges from mm → cms
- Variable wall thickness
- Air- fluid level ⇒ indicates bacterial / fungal super infection .

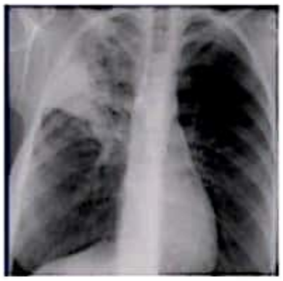
C. TB Bronchopneumonia



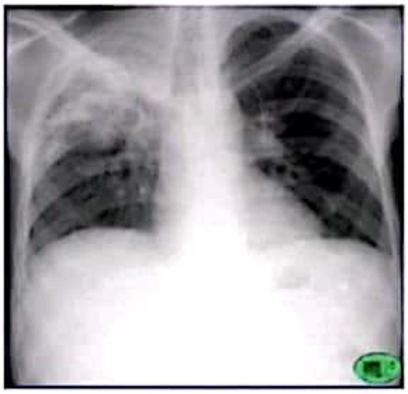
Both lungs - Disseminated Nodular opacities

- more common in middle and Basal lung fields
- moderate intensity
- Different size

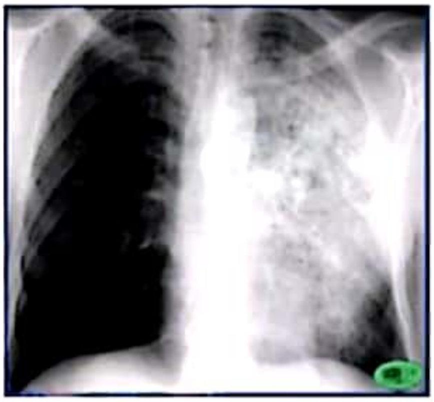
d. TB - pneumonia



Triangluar opacity - localised to Right Upper Lobe [RUL]



Segmental infiltrate involving entire RUL



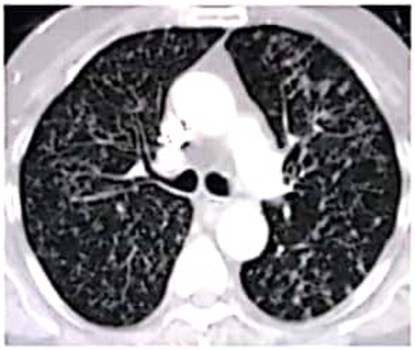
massive left pneumonia

e. Tree -in- bud appearance

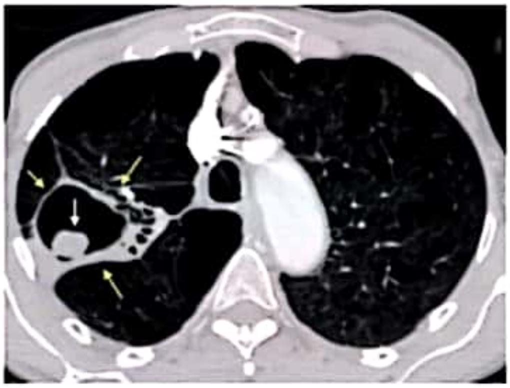
- seen in post 1°TB
- HR-CT ⇒ multiple small, centrilobular nodules connected to linear branching opacities

f. Aspergilloma

- post - TB cavity with a fungal ball



Tree-in-bud appearance



3. Secondary TB - Complications

i) Fibrocaseation ⇒ fibrosis

ii) Aneurysmal rupture ⇒ Bleeding
 Rasmussen's aneurysm [pulmonary artery aneurysm]

iii) TB empyema

iv) Pleural thickening

v) Lung abscess / necrotising pneumonia

vi) Bronchopleural fistula

Miliary tuberculosis

00:39:40

- Infective foci in the lung

⇓

seeds in pulmonary venous system

⇓

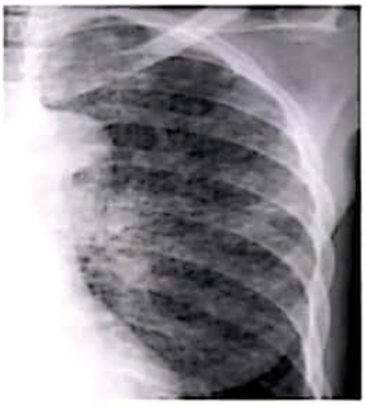
Liver, Bone marrow, Spleen, Adrenals

- Pathognomic features of miliary TB ⇒ Choroid Tubercles .
- Occurs in both 1° & 2°
- Often sputum negative
- Steroid unresponsive

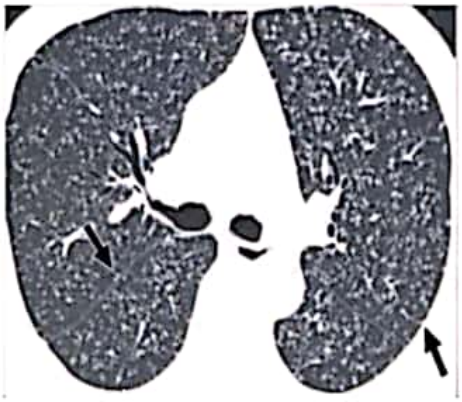
- Miliary TB

Sub-acute >> Acute

- Patient present with – fever, anaemia, weight loss.
- X-ray → numerous millet size opacities [2-3mm nodules]



X-ray – lung – miliary opacity



CT – lung – miliary opacities

a. Cryptic miliary TB
  - elderly
  - chronic course
  - meningeal involvement

b. Non-reactive miliary TB
  - Fatal
  - immunocompromised individuals
  - no granuloma formation
  - necrosis of the lung

Extra- pulmonary TB

00:44:25

- most common extra pulmonary TB → lymph node TB
- most common LN involved → post cervical TB
- most common reproductive organ involved in males → Epididymis
- most common site of spinal TB

Adults $T_{12} - L_1$

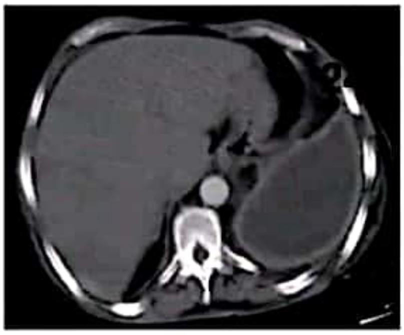
children $T_9 - T_{10}$

- IOC [Investigation Of Choice] in tuberculous meningitis→ GENE-XPERT
- Gastric- TB most commonly involves → ileum
- most fatal → TB pericarditis

Note

a. Split – pleura sign

- seen with pleural empyema
- most reliable CT sign – to distinguish empyema from peripheral pulmonary abscess

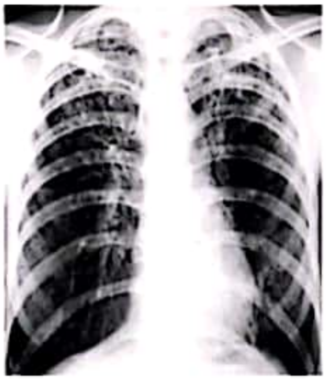


b. Parenchymal post – primary TB

- crowding of the ribs
- parenchymal post – primary TB

$\Downarrow$

fibrosis



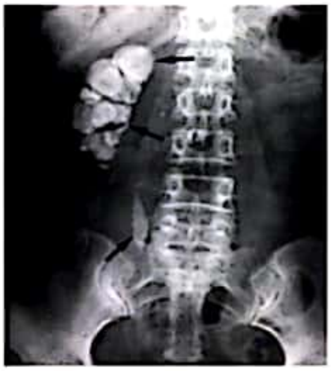
B/L upper lobe fibrosis

c. Renal TB

- Cummulus cloud calcification
- Putty Kidney
- Thimble bladder
- Hiked up pelvis
- Golf – hole ureter
- Pipe stem ureter

Symptoms

- asymptomatic acid sterile pyuria
- recurrent lower urinary tract obstruction
- recurrent Urinary Tract Infection [UTI]



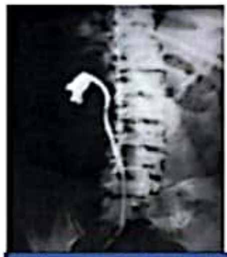
Putty Kidney

X-ray – Kidney

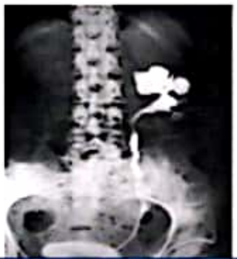
i) Putty Kidney

- Autonephrectomy state ,
- also known as putty kidney or cement kidney
- multiple calcification forming a cast

ii)

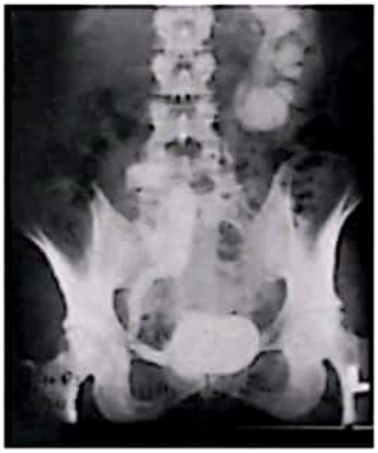


Calyceal occlusion due to complete Fibrosis Rigid fibrotic ureter



Diffuse calyceal distortion Multiple ureteric strictures

iii) Thimble bladder



- Small irregular contracted bladder

Sputum smear direct microscopy

00:00:41

- AFB Staining – (Acid fast bacili)
- Oil immersion microscopy.
- Has Low sensitivity – < 50 %
- BAL specimens (Bronchoalveolar lavage)

↓

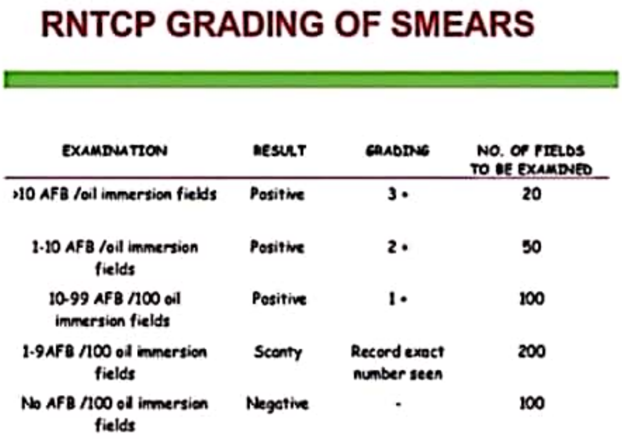
obtained after nebulised hypertonic saline / bronchoscopy

↓

↑ secretions – ↑ sputum.

↓

↑ sensitivity – 60–70 %



RNTCP GRADING OF SMEARS

EXAMINATION	RESULT	GRADING	NO. OF FIELDS TO BE EXAMINED
>10 AFB /oil immersion fields	Positive	3+	20
1-10 AFB /oil immersion fields	Positive	2+	50
10-99 AFB /100 oil immersion fields	Positive	1+	100
1-9AFB /100 oil immersion fields	Scanty	Record exact number seen	200
No AFB /100 oil immersion fields	Negative	-	100

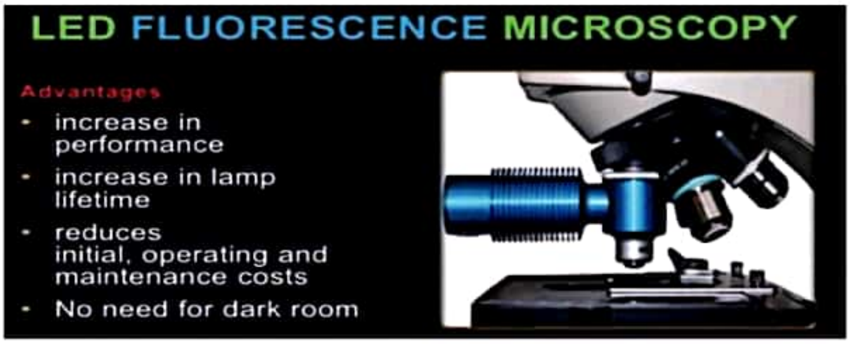
- minimum 10^4 (10,000) organisms/ ml of sputum is required for sputum smear direct microscopy

LED fluorescence microscopy

- Better technique for diagnosis
- Can be done using

↓ Auramine – O

↓ Auramine – O
Rhodamine – B



LED FLUORESCENCE MICROSCOPY

Advantages

- increase in performance
- increase in lamp lifetime
- reduces initial, operating and maintenance costs
- No need for dark room

Automated culture- WHO recommended 00:07:44

- 100 organisms/ml of sputum is required
- Takes 10-12 days to grow the organism
- Also detects drug Susceptibility
- Two types

Radiometric
↓
- BACTEC 460

Non Radiometric
↓
- MGIT 960
- MB/ BacT

MYCOBACTERIAL GROWTH INDICATOR TUBE (MGIT)

- Positive signals are obtained in 10-12 days. MGIT can also be used as a rapid method for the detection of drug resistant strains of Mtb directly from acid-fast smear positive samples as well as from indirect drug susceptibility studies.
- Advantages over BACTEC
- Cheaper.
- No problem of radioactive waste disposal.

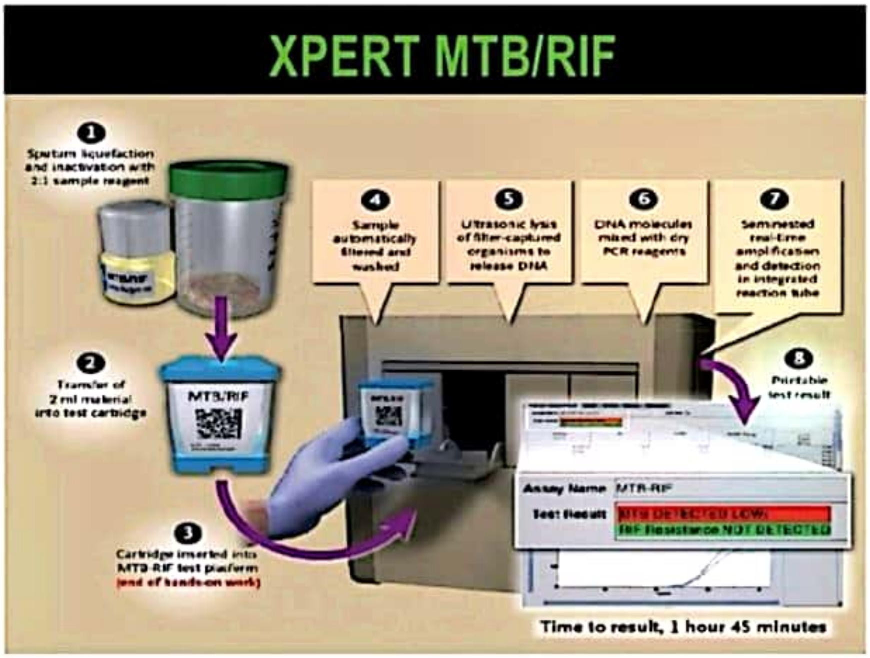
Gene xpert- CBNAAT 00:10:24

- CB NAAT - MTB / Rifampicin (RIF) assay
- Time taken - 1 hr 45 mins
- Initial diagnostic test for children & adults with HIV
- Used in extrapulmonary TB
- 70% Sensitivity in AFB negative
- 98% Sensitivity in AFB positive
- I.O.C for - Cerebrospinal fluid & gastric lavage sample
- Not useful in pleural effusion sample - cannot detect myobacterium

↓

hence pleural biopsy performed

Active space


XPERT MTB/RIF
1 Sputum liquefaction and inactivation with 2:1 sample reagent
2 Transfer of 2 ml material into test cartridge
MTB/RIF
3 Cartridge inserted into MTB-RIF test platform (end of hands-on work)
4 Sample automatically filtered and washed
5 Ultrasonic lysis of filter-captured organisms to release DNA
6 DNA molecules mixed with dry PCR reagents
7 Seminested real-time amplification and detection in integrated reaction tube
8 Printable test result
Assay Name MTB-RIF
Test Result MTB DETECTED LOW; RIF Resistance NOT DETECTED
Time to result, 1 hour 45 minutes

Xpert MTB/RIF from different samples

SAMPLE	SENSITIVITY	SPECIFICITY
Sputum	88%	99%
Lymph node aspirate	84.9%	92.5%
CSF	79.5%	98.6%
Pleural fluid	43.7%	98.1%
Gastric lavage/aspirate	83.8%	98.8%

Gene xpert - uses and properties

00:16:10

- It is a molecular / genotypic method for the diagnosis of tuberculosis
- It is a real time PCR
- Approximately 2ml of sample is required
- Procedure time less than 2 hours (1hr 45mins)
- It allows rapid screening of rifampicin resistance (rpoB mutation)
- Detects only MTB complex (thus it can differentiate MTB and NTM)
- Detects both live and dead bacilli
- Semi- quantitative and fully automated
- Closed system (no contamination risk)
- Applicable to any body fluids excepts blood, urine and stool
- Useful for the diagnosis of tuberculosis and rifampicin resistance in pediatric age
- Useful in HIV patients, paucibacillary cases and extrapulmonary cases

Active space

Line probe assays

00:18:08

- Done only in Sputum AFB positive cases
- Results obtained within 48- 72 hrs
- PCR based technique
- Advantage - detects KatG & Rifampicin (rpoB) resistance
- Time to diagnose MDR TB (multi drug resistant) reduced to 7days
- Lipoarabinomannan (man- LAM) detection in urine

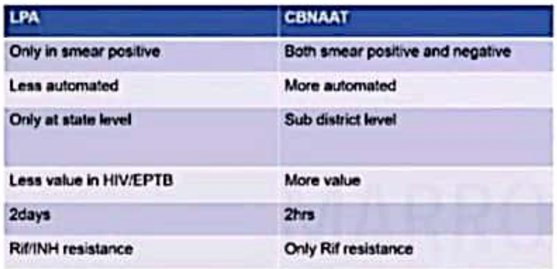
Sputum smears
↓
AFB ↓ oil immersion microscopy

Smear positive
↓
Line probe assay
(48-72 hrs)
INH/ RIF resistance

Smear negative
↓
CBNAAT
↓
MTB/ Rifampicin resistance
if Positive → BACTEC / MGIT

RIF resistant

No resistance



LPA	CBNAAT
Only in smear positive	Both smear positive and negative
Less automated	More automated
Only at state level	Sub district level
Less value in HIV/EPTB	More value
2days	2hrs
Rif/INH resistance	Only Rif resistance

Latent tuberculosis infection

00:23:35

- Diagnosis - Tuberculin Skin test

↓
After 6- 12 weeks of exposure if positive
↓
Indicates Latent TB

- Technique - PPD (Purified protein derivative) - Tuberculin / RT- 23

0.1 ml/ 5 IU
given intradermally
↓

Induration depth after 72 hrs

≥ 5 mm → Significant in →
i) HIV patients
ii) Post transplant
iii) Recent contact with TB
IV) Steroids / anti TNF
v) fibrotic lesions Consistent with old TB

5- 15 mm → Significant in →
- Laboratory person
- IV drug abuser

≥15 mm → Significant in low risk/ normal patient

- management - Isoniazid prophylaxis → 6- 9 months

Warning : Not all points are covered in the notes, especially conceptual explanations. Please use the notes in conjunction with marrow Edition 4 videos.

Tuberculin skin - false positive and false negative skin test 00:29:51

False positive MT (mantoux test)
- Sensitivity induced by environmental Non tuberculous mycobacteria (NTM)
- Sensitivity induced by previous BCG vaccination
- High dose of Tuberculin
- Repeat testing - Boosting phenomenon
- Reading error

False negative (MT)
- Improper storage or technique of administration of tuberculin
- Reading error
- Infants < 3 months age (immature immune System)
- Old age (generalised suppression of cell mediated immunity

False positive MT conditions	False negative MT conditions
• Disseminated / miliary TB • Viral infections – measles, chickenpox • MT done within the window period (8 weeks of exposure of MTB)	• Anergy • malnutrition • Immunosuppression

Interferon Gamma Release Assay (IGRA)

↓ Quantiferon gold ↓ T- spot test

Quantiferon gold ↓

- more specific
- Tuberculin skin test is preferred over IGRA ↓ in children

- IFN γ released in response to recirculating T-cells ↓ Antigens – ESAT – 6, CFP- 10

- Incident active TB/ Risk of progression/ no drug susceptibility/ poor Sensitivity

TUBERCULOSIS - MANAGEMENT

Terms in Tuberculosis 00:00:36

1. Drug susceptible case
   - Those susceptible to Anti-TB drugs

2. Drug resistant case
   - Resistance to Isoniazid (INH) alone
   - Resistance to INH + R (Rifampicin)

3. Definitions : (outdated terms)
- New – New case or treatment < 1 month
- Relapse – patient who is declared cured & has reinfection
- Failure – At the end of 5 months in case of smear positive case & at the end of 2 months in case of smear negative case

  ⇓

  If the smear is still positive

  ⇓

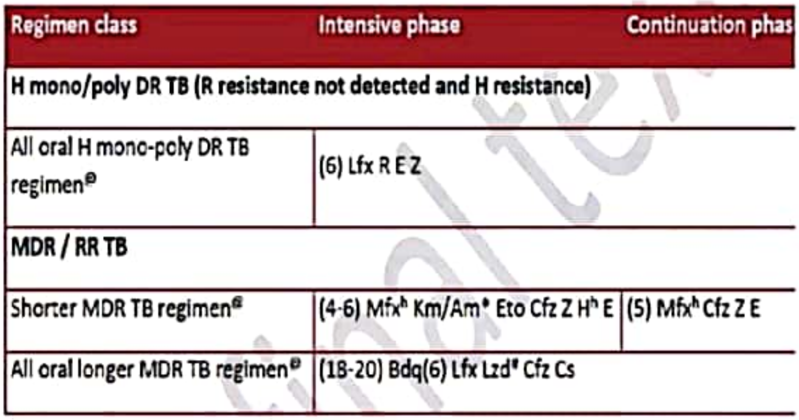
  Failure
- Default – Treatment skipped for > 2 months
- Cured – Patient is smear negative
- Chronic case – TB with chronic complication (Eg – Fibrosis)
- Completed Treatment – Patient has completed the treatment schedule
  - may or may not be cured

Treatment of drug susceptible & drug resistant TB 00:05:56

	Intensive Phase	Continuous Phase
1. Drug susceptible	HRZE x 2 months	4 HRE
2. Drug resistance i) INH resistant	Lfx RZE x 6 months	
ii) INH + R resistant [longer Regime ↓ Preferred]	Levofloxacin Linezolid Cycloserine Clofazimine } x 18–24 months + Bedaquiline x 6months	

Newer drugs

- Bedaquiline → mycobacterial ATP synthase inhibitor
  Dose : 400 mg/day x 2 weeks and
  continue to 200 mg/day x 22 weeks
- Delamanid → mycolic acid synthesis – inhibitor



Regimen class	Intensive phase	Continuation phas
H mono/poly DR TB (R resistance not detected and H resistance)		
All oral H mono-poly DR TB regimen$^{@}$	(6) Lfx R E Z	
MDR / RR TB		
Shorter MDR TB regimen$^{@}$	(4-6) Mfx^{h} Km/Am* Eto Cfz Z H^{h} E	(5) Mfx^{h} Cfz Z E
All oral longer MDR TB regimen$^{@}$	(18-20) Bdq(6) Lfx Lzd$^{\#}$ Cfz Cs	

Regime for treatment of multi Drug Resistant – (MDR) – TB
or
mono – Poly DR – TB (Drug Resistant – Tuberculosis)

Daily Dosing

H / INH (Isoniazid) → 5 mg / kg
R (Rifampicin) → 10 mg / kg
Z (Pyrazinamide) → 25 mg / kg
E (Ethambutol) → 15 mg / kg

Bedaquiline → monitoring of QT interval daily

HIV & TB

00:12:54

- most common opportunistic infection in HIV patients occuring at a CD – 4 count of 300 early in the course
  ⇓
  TB
- Relative risk of reactivation of TB in HIV patient is 100%
- Drug resistant TB are more common
- Reason for TB in HIV
  - ↓ Th$_1$ response
  - ↓ Interferon γ

Active space

Concerns with Tb in HIV

1) Latent TB

- TST (Tuberculin skin Test > 5 mm) ⇒ Latent TB

(or)

- Interferon Gamma Release Assay (T-spot) ⇒ positive

- Treatment - INH x 9 months

2) 70% → sputum negative [∴ Do xpert MTB / RIF]

> 50% → extrapulmonary

3) CD-4 > 200 ⇒ Typical [Cavitating 2° TB]

CD-4 < 200 ⇒ Atypical [1° TB - like pattern]

Lower lobe infiltrates + No Cavity + Focal consolidation

- In HIV → PUO (Pyrexia of unknown Origin) + Weight loss is due to TB unless proven otherwise

Treatment of TB in HIV

- Regime → HRZE x 2 months + HRE x 7 months [Total - 9 months]
- INH prophylaxis x 9 months ⇒ ↓ risk of reactivation

1) TST - ⊕ with HIV infection has 10% risk every year for development of active TB

TB in HIV & Anti-Retroviral Therapy [ART] 00:19:37

1. Latent TB positive

INH x 9 months

2. HIV + TB infection

i) CD_4 < 200 → ART within 2 weeks of starting ATT [Anti-TB therapy]

ii) CD_4 > 200 → ART within 8 weeks starting ATT

iii) Cotrimoxazole prophylaxis to all HIV - TB cases to prevent Pneumocystis jirovecii pneumonia

- ART regime

(Lamivudine) NRTI + Tenofovir [nucleotide reverse transcriptase inhibtor] + Efavirenz

- Protease inhibitor is not used

[Reason - metabolism of protease inhibitor can be induced by rifampicin (CYP 450 3A)]

- Nevirapine is not used [Reason - hepatotoxic]

- Thioacetazone → fatal Steven Johnson Syndrome

- TB screening –
  - Smear test
  - BAL (Broncho Alveolar Lavage) / sputum test
  - CBNAAT
  - X- ray

Immune Reconstitution Inflammatory Syndrome [IRIS]

00:24:14

Risk factors for IRIS

- Low baseline CD$_4$ count
- Higher baseline viral load
- Shorter interval between commencing ATT & HAART
- Disseminated TB
- A greater reduction in viral load after starting HAART

Suspect IRIS

After commencing ART

- Fever, anaemia, weight loss
- CNS conditions
- Lymphadenopathy
- New or exacerbation of already existing pulmonary lesion
- New or worsening radiological features

- IRIS → Paradoxical worsening of clinical symptoms in an HIV patient
  [Reason – Immune restoration]
  - → seen in 10–20 % cases, with initiation of ART at a low CD$_4$ count
  - → within 12 weeks of HAART [↓ viral RNA]
- Treatment → Steroids

COMMUNITY ACQUIRED PNEUMONIA

Community acquired pneumonia 00:01:30

- Acute infection of pulmonary parenchyma.
- Causative organism :
  - → Streptococcus pneumoniae (pneumococci) mc
  - → Hemophilus influenza (2nd mc)
  - → mycoplasma pneumonia
  - → Chlamydia pneumonia
- Rare :
  - → Legionella
  - → Staphylococcus aureus.
  - → Gram negative organism (Klebsiella, pseudomonas)
  - → Virus
- In India 20% cases of CAP → Tuberculosis
  40% cases of CAP → Not established.

Causes of community acquired pneumonia 00:06:55

Out patient	Inpatient	ICU
- Pneumococci (mc overall)	- Pneumococci	- Pneumococci
- H. influenza	- H. Influenza	- MRSA
- mycoplasma	- mycoplasma	- Pseudomonas
- Chlamydia	- Legionella Pneumonia	- Legionella

Pathogenesis of CAP 00:10:06

Occurs due to defective →

- Pulmonary alveolar macrophages.
- Cell mediated immunity.
- Exudative capillary leak → localised consolidation.
- Features :
  - High grade fever mediated by → IL-1 & TNFα
  - ↑ Vocal fremitus, ↑ Vocal resonance
  - Tubulobronchial breathing
  - Egophony
  - Whispering pectoriloquy
- Percussion → Dull note.

- Impairment of oxygenation across alveolar capillary membrane – Hypoxia
- IL – 8 Stimulates release of neutrophils.
- Complication – Type I Respiratory failure.
- Bad prognosis – Hypothermia
  Leukopenia.

Pathological stages of lobar pneumonia 00:19:00

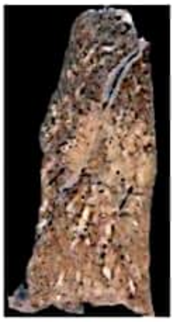
- Phases :

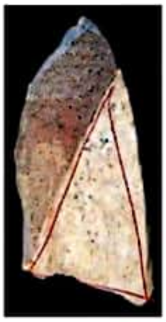
→ I) congestion : 1 – 2 days
bacteria with proteinaceous exudates.

→ II) Red hepatization : 3–4 days.
Neutrophilic exudates.

→ III) Grey hepatization : 5–7 days.
Fibropurulent exudates
(No organism seen)

→ IV) Resolution after 7–8 days.
Infiltration of machrophages





CAP

Typical / Lobar Pneumonia
↓
- Lobar consolidation
- Causative organism
  Pneumococci
  H. Influenza
  Staph aureus
  Klebsiella
  Pseudomonas.

Atypical / Interstitial/ Broncho pneumonia
↓
- Patchy interstitial inflammation.
- Causative organisms:
  chlamydia
  mycoplasma

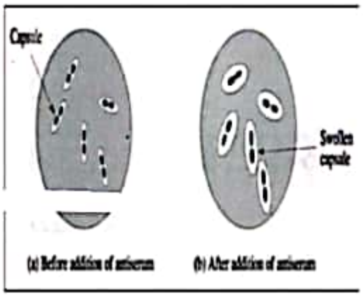
→ Legionella → both typical & atypical presentation.

Pneumococci 00:24:42

- MC Organism causing pneumonia.
- Gram positive cocci
- α Hemolytic
- Catalase Negative.

LANCEOLATE
DIPLOCOCCI

- Fastigious growth requirements
- Flame / Lanceolate shaped diplococci
- Blood Agar → Draughtman or carrom coin appearence. Greenish colonies due to partial (α) Hemolysis.


Capsule
Swollen capsule
(a) Before addition of antiserum
(b) After addition of antiserum

- Rapid identification : Quellung reaction (Swollen capsule after addition of antiserum]
- Adherence to nasopharynx / invasion seen only with serotype ?

- Differentiating features of pnemococcus from S. viridans →
  - Bile solublity
  - Option sensitivity.
  - Inulin fermentation.

- Virulance factors →
  - Capsular polysaccharide
  - Pneumolysin
  - IgA, protease.

- Abnormal protein which precipitates with somatic C antigen → C Reactive protein.
- Cytolytic toxin which forms pores in cell membrane is Pneumolysin.

Risk factors and vaccination of pneumonia 00:31:40

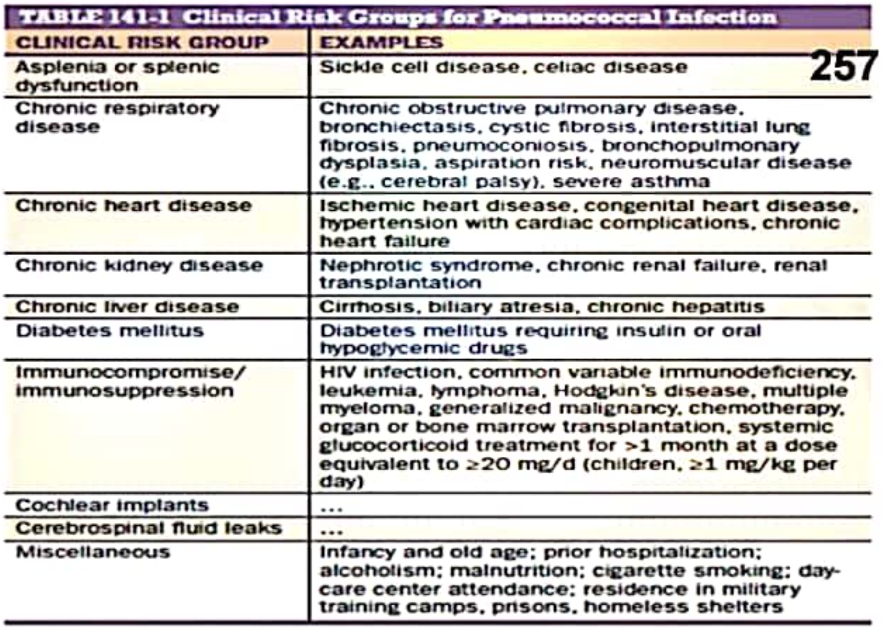
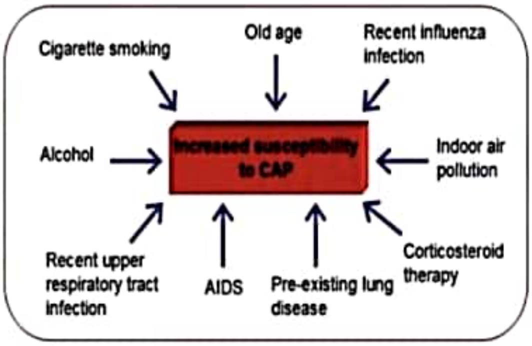


TABLE 141-1 Clinical Risk Groups for Pneumococcal Infection

CLINICAL RISK GROUP	EXAMPLES
Asplenia or splenic dysfunction	Sickle cell disease, celiac disease
Chronic respiratory disease	Chronic obstructive pulmonary disease, bronchiectasis, cystic fibrosis, interstitial lung fibrosis, pneumoconiosis, bronchopulmonary dysplasia, aspiration risk, neuromuscular disease (e.g., cerebral palsy), severe asthma
Chronic heart disease	Ischemic heart disease, congenital heart disease, hypertension with cardiac complications, chronic heart failure
Chronic kidney disease	Nephrotic syndrome, chronic renal failure, renal transplantation
Chronic liver disease	Cirrhosis, biliary atresia, chronic hepatitis
Diabetes mellitus	Diabetes mellitus requiring insulin or oral hypoglycemic drugs
Immunocompromise/ immunosuppression	HIV infection, common variable immunodeficiency, leukemia, lymphoma, Hodgkin's disease, multiple myeloma, generalized malignancy, chemotherapy, organ or bone marrow transplantation, systemic glucocorticoid treatment for >1 month at a dose equivalent to ≥20 mg/d (children, ≥1 mg/kg per day)
Cochlear implants	...
Cerebrospinal fluid leaks	...
Miscellaneous	Infancy and old age; prior hospitalization; alcoholism; malnutrition; cigarette smoking; day-care center attendance; residence in military training camps, prisons, homeless shelters

1) COPD / Smoking
2) T_2DM – 10 years
3) Chronic liver disease
4) CKD
5) Asplenia
6) HIV / Immunocompromised.
7) Serious immunosuppression.
8) Steroids.
9) Age > 65 years.


Cigarette smoking
Old age
Recent influenza infection
Alcohol
Increased susceptibility to CAP
Indoor air pollution
Recent upper respiratory tract infection
AIDS
Pre-existing lung disease
Corticosteroid therapy

Types of vaccine .

PCV – 13
(Pneumococcal conjugate vaccine)

PPSV – 23
(Pneumococcal polysaccharide vaccine)

- Age < 65 years / immunocompromised → PCV – 13 (single dose
  ↓ After 8 weeks
  PPSV – 23
- Age < 65 years with T_2DM → PPSV – 23 (single dose)
- Age > 65 years → PCV – 13 single dose.

Clinical presentation 00:36:33

- Acute onset.
- Fever
- Cough + Sputum
- Tachypnoea, Tachycardia
- Pleuritic chest pain

- On examination :
  - Tubulobronchial breathing
  - ↑ Vocal fremitus, vocal resonance.
- Dyspnea → Hypoxia → Respiratory failure (rare)
- In elderly / immuno compromised →
  1) Altered mentation
  2) Acute abdominal pain
  3) Persistent hiccoughs

  } Rule out pneumonia

Mycoplasma/ interstitial/atypical pneomonia 00:40:17

- MC bacteria causing Atypical pneumonia.
- 2nd MC cause of pneumonia .
- No cellwall / No flagella
- Sterol's on cell membrane.
- Smallest free living organism capable of replication.
- On PPLO Agar → (Dienes method)
  Biphasic with fried egg appearance
- Clinical symptom :
  - Very non specific presentation .
  - 10 % present as pneumonia .
  - URTI (Tracheobronchitis / Pharyngitis)

Extra pulmonary manifestations :
1) Cold agglutinin disease (Igm mediated AIHA)
2) Erythema multiforme / SJS
3) Arthralgia + adenopathy
4) Guillain Barre syndrome.
5) myocarditis / Pericarditis .
6) Encephalitis .
7) Bullous meningitis

Investigations :
1) PCR of respiratory secretions.
2) Chest X Ray :
   - Patchy consolidation at hilum
   - Fanning to periphery .

management :
DOC : Azithromycin
2nd best : Doxycyclin .

Lobar pneumonia v/s atypical pneumonia

00:46:07

Lobar pneumonia	Atypical pneumonia
Extra cellular organism.	Intracellular organism.
Alveolar exudates in air spaces.	Interstitial involvement
Neutrophilic	Lymphocytic
High grade fever	Low grade fever.
Productive cough	Dry cough
Hemoptysis +	Scanty sputum.
Pleuritic chest pain	Extrapulmonary manifestation
X Ray → Large areas of consolidation	X Ray → Interstitial pattern.

Note :

- MC organism causing pneumonia- S.pneumoniae
- MC organism causing bacteremia/sepsis- S.pneumoniae
- MC organism causing pneumonia in alcoholic- S.pneumoniae > anaerobes > Klebsiella
- MC organism causing pneumonia in patients with altered level of conciousness, dementia, gingivitis (have high chance of aspiration), stroke--> anerobes
- Mc cause of complicated pneumonia → S. Pneumonia
- MCC of bacteremia in diabetic → S. Pneumonia.
- Association with Hemolytic anemia / SJS/GBS → mycoplasma
- Mc in unerlying structural lung disease / COPD / Bronchiectasis → Pseudomonas.
- Pneumonia associated with atherosclerosis → Chlamudia pneumonia.
- Pneumonia associated with dairy farms, amniotic fluid, placenta → Q fever [Coxiella burnetti]
- Klebsiella pneumonia associated with.
  - Alcohol
  - Upper lobe
  - Cavitation
  - Pneumatocele (also seen in S.aureus)
  - Bulging fissure sign → Klebsiella pneumonia .
- Exposure to :
  1 Bats → H . Capsulatum
  2 Birds → Chlamydia pneumonia

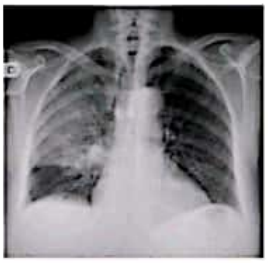
  3 Rabbits → F. Tularemia.

Investigations

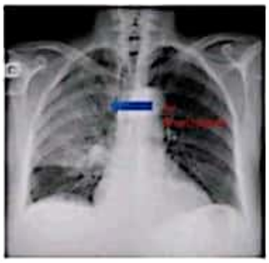
00:52:13

Chest X ray :

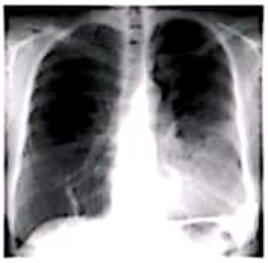
- No destruction of lung parenchyma
- Fluffy opacities present



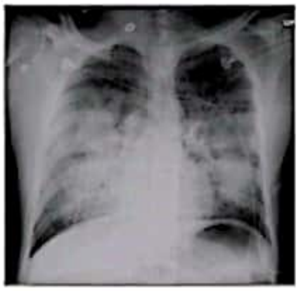
- Air bronchogram → indicative
- Of Lobar consolidation

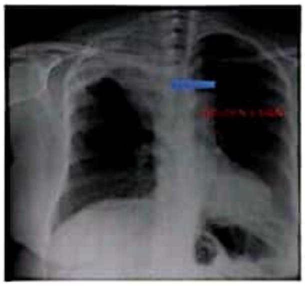


- " Silhouette sign "



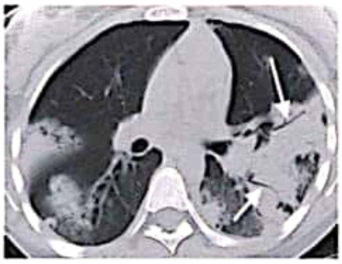
- Lobar density in upper lobe
- Golden ' s ' sign [Reverse S sign of Golden]
- Batwing appearance → Cardiogenic Pulmonary edema .





CT Scan :

- Consolidation with air bronchogram .



Conditions associated with air bronchogram :

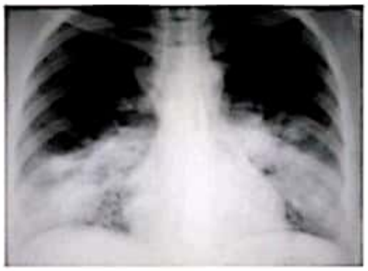
1) Pulmonary consolidation .
) Pulmonary edema
3) Non obstructive atelectasis .
4) Severe interstitial lung disease .
5) Neoplasm.
6) Pulmonary infarct .
7) Pulmonary Haemorrhage .
8) Normal expiration .

Chlamydia pneumoniae 00:59:44

- Obligate intracellular bacteria
- Peptidoglycan → absent .
- Prolonged asymptomatic condition of upper respiratory tract .
- Isolation : Hep 2 cells .
- Elementary body → metabolically inactive extracellular infection form [DNA = RNA]
- Associated with atherosclerosis .
- Extrapulmonary manifestations – minimal compared to mycoplasma
- Gold standard : Serology (micro immunofluorescence test)
- Specific investigation – PCR
- Person to person spread via droplets .
- Intrinsically resistant to sulphonamides .
- management : Azithromycin (DOC)
  Doxycycline .
  Respiratory quinolones .

Legionella pneumonia 01:03:52

- Gram negative, partially acid fast aerobes .
- motile, Intracellular.
- Grows in Buffered Charcoal Yeast Extract (BYCE) medium .
  2 aquatic bodies / forms microcolonies within biofilms .
- mode of spread → microaspiration >> aerosolization .
- mild disease → Pontiac fever
- Severe disease → Legionnaires disease .
- Risk factor :
  1 Smoking
  2 Hairy cell leukemia
  3 Disruption of cell mediated immunity .



- Typical presentation :
  - High grade fever
  - Bilateral dense lower lobe consolidation
  - leucocytosis
  - Productive cough .
  - Rapidly progressive .

- Atypical presentation :
  - Non Productive cough
  - Hyponatremia
  - Diarrhoea
  - Hepatic involvement → ↑ Enzymes
  - Hematuria
  - Thrombocytopenia .
- Organism cannot be cultured from sputum .
- MC Extrapulmonary Legionellosis → Heart .

Investigations and management

01:09:46

1) culture of transtracheal aspirate – Best test
   90% → Sensitivity .
   100% → Specificity .
2) Urinary antigen testing
   100% → Specificity .
   LOW → Sensitivity .

3) Direct fluorescence antibody staining of sputum (100% Specificity)

Management :
- Macrolides (Azithromycin) + Rifampicin .
- Respiratory quinolones .

Diagnostic indications for community acquired pneumonia 00:00:13

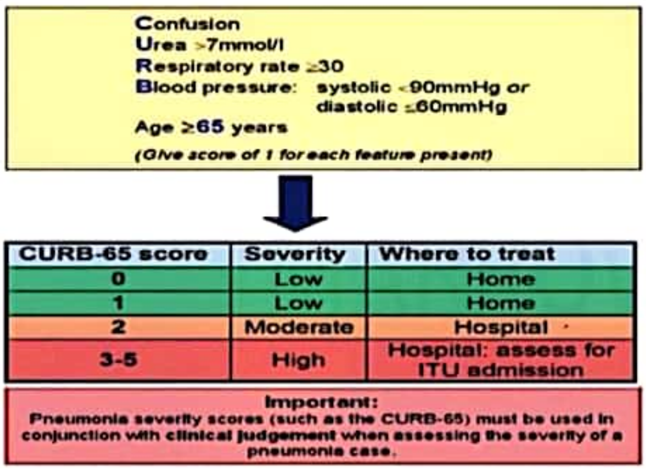
1 Fever, cough, pleuritic pain → dyspnoea
2 Extra pulmonary feature + upper Respiratory tract infection.
3 Elderly patients with altered sensorium.
4 Hiccups or acute abdominal Pain.

Investigations :
1 Culture & Sensitivity :
  - Sputum
  - Blood → 30%
2 Urinary Legionella Antigen
3 Chest X Ray
4 CT - Chest

CURB - 65 Score 00:02:18

- modification of British Thoracic Society (BTS) rule in assessing Pneumonia mortality risk.
- Variables :
  1 Age ≥ 65 years.
  2 Confusion.
  3 Blood Urea nitrogen ≥ 7 mmol / lt or 20mg / dl
  4 Respiratory Rate → > 30 / min.
  5 Blood Pressure < 90 / 60 mmHg.

- Score :
  0 - 1 → managed at home
  2 → Admission.
  3 → ICU management.



Confusion
Urea >7mmol/l
Respiratory rate ≥30
Blood pressure: systolic <90mmHg or
diastolic ≤60mmHg
Age ≥65 years
(Give score of 1 for each feature present)

CURB-65 score	Severity	Where to treat
0	Low	Home
1	Low	Home
2	Moderate	Hospital
3-5	High	Hospital: assess for ITU admission

Important:
Pneumonia severity scores (such as the CURB-65) must be used in conjunction with clinical judgement when assessing the severity of a pneumonia case.

Treatment of Community Acquired Pneumonia.

Score - 0

Doc : macrolides.

- Azithromycin 500mg OD

  or

- Clarithromycin 500mg BD

  or

- Doxycyclin 100mg BD

Score - 1

- Azithromycin 500mg OD + Ceftriaxone 2gm OD
- Respiratory quinolones - not preferred.
  Levofloxacin 750 mg IV OD - now not Preferred.

Score > 2 (ICU)

- Azithromycin 500mg OD + Ceftriaxone 2gm IV OD
- Specific management.

→ Drug resistance to empirical treatment can be due to :

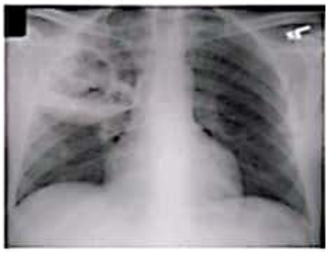
1 Gram negative organisms. [Klebsiella, Pseudomonas]
2 MRSA (Doc : Vancomycin)
3 Anaerobes (Doc : Clindamycin)

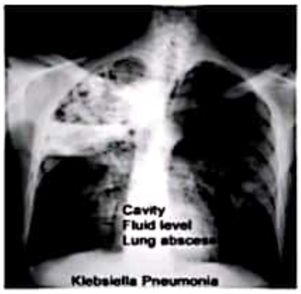
COMPLICATIONS OF CAP

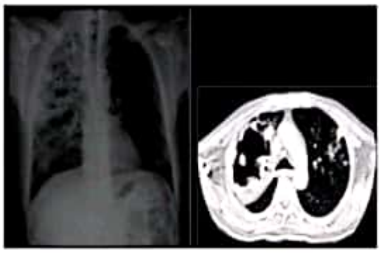
Complications of Community Acquired Pneumonia (CAP) 00:00:16

- If symptoms does not subside even within 24-48 hours of antibiotics.
  - → Resistance due to :
    - → Gram negative organisms
    - → Anaerobes
    - → MRSA

Bulging fissure sign







(1) Lung Abscess / Necrotizing pneumonia

- MC complication
- Localised area of infection causing Suppurative parenchymal necrosis
- MC causative organism → Anaerobes
- Cause :
  - Aspiration
  - Immunocompromised
  - ICU patients
- Features :
  - Fever, chills with subacute presentation
  - Weight loss
  - Cough ± foul smelling sputum
  - Hemoptysis
  - Clubbing
  - Prostration / lassitude
  - Tachypnea / impaired percussion
  - Bronchial breathing
    - → Consolidated, necrotising and suppurative area opens into draining bronchus with purulent expectoration and abscess with ' Air fuid level '
- MC site → superior segment of lower lobe

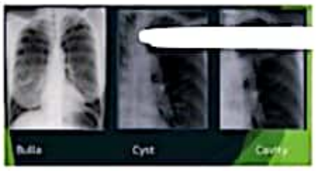
. On percussion : Succussion splash , cracked pot resonance, coin test positive.

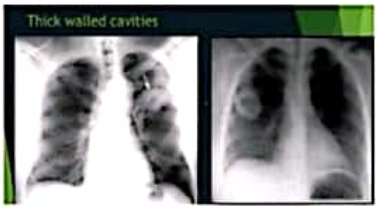
. Cavity connected to a patent bronchus on auscultation :

- Deep-seated cavity : Cavernous breath sounds
- superficial cavity : Amphoric breath sounds

On X-Ray :

- Thick wall lung cavity seen
- Air fluid level seen
- Bulging fissure sign

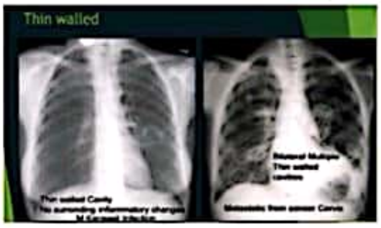




Causes of thick wall lung cavity :

- > 2mm thickness

(1) Wegener's granulomatosis
(2) Squamous cell carinoma of lung.
(3) Blastomycosis
(4) Histoplasmosis



- Thin wall cavity :

Infective	Noninfective
- Tuberculosis	- Rheumatoid arthritis
- Anaerobes	
- Gram -ve bacteria	

- ↑ risk of aspiration → Alcoholics [dementia]
  - Site of aspiration depends on position of aspiration
- Supine position affects →
  - Superior segment of right lower lobe
  - Posterior segment of right upper lobe (mc)
- Sitting position affects →
  Basal segment of lower lobe
- Secondary lung abscess : Obstruction, tumour

Complication :

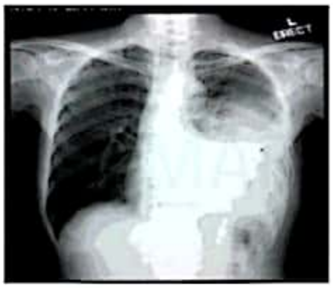
(1) Bronchopleural fistula.
(2) Pyopneumothorax.
(3) Secondary amyloidosis.

Management :

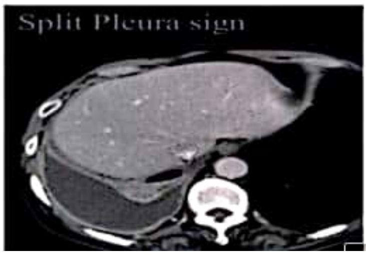
- 6-8 weeks of Antibiotics
- Preferred drug : clindamycin

Empyema

00:05:34



- 2nd MC complication
- Pus in pleural cavity
- Pleural fluid :
  ↓ pH
  ↓ glucose
  ↑ LDH
- On CT : Split pleura sign
- Fluid between parietal and visceral pleura
- Management :
  Emergency ICT drainage


Split Pleura sign

Indication for ICT drainage :
* Low pleural fluid pH
* Glucose in pleural fluid is low
* Increased LDH

On chest x-ray :
Empyema thoracic – cloudy or opaque area.

Difference between (On CT scan)

Abscess	Empyema
– Thick irregular wall	– Lentiform
– Acute angle to chest wall	– Smooth wall
	– Obtuse angle to chest wall
– Surrounding consolidation +	– No surrounding consolidation
	– Split pleura sign

Other complications of CAP :
(1) ARDS
(2) Type I respiratory failure
(3) Sepsis
(4) myocarditis
(5) DIC

Warning : Not all points are covered in the notes, especially conceptual explanations. Please use the notes in conjunction with Marrow Edition 4 videos.

H1 N1 - Swine flu 00:17:56

- Flu like symptoms and persistent dry cough with sore throat
- Risk factor :
  - Immunocompromised
  - Pregnancy
- Bad prognostic indicators :

① Leukopenia
(2) Creatine phosphokinase – Rhabdomyolysis
(3) Hypothermia

Investigation :
- Throat swab for viral PCR
- X – ray : Diffuse bilateral infiltrates

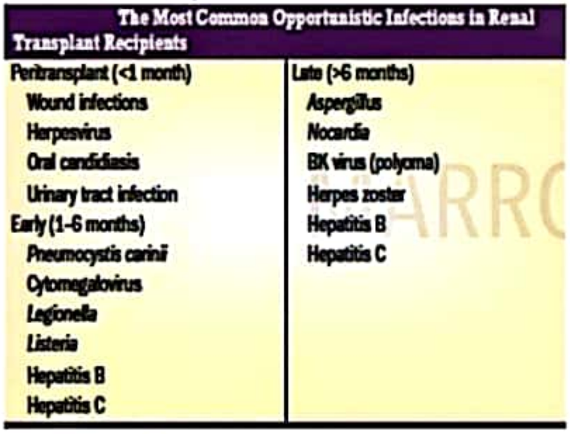
management :
DOC : Oseltamavir 75 mg BD.

Severly immunocompromised : 1) Neutropenia
a) post transplant patient
(Hematopoetic stem cell transplant (HSCT), solid organ transplant)
3) High dose steroid
[> 30mg / day for >3 weeks]

Lesser degree of immunosuppression :
- Type II DM
- elderly
- Chronic Kidney disease (CKD)
- chronic liver disease (CLD)
- myeloma

Infections in immunocompromised patients 00:02:09

- Gram negative organisms : pseudomonas, Klebsiella, Nocardiosis
- Fungal : Pneumocystis jirovecii pneumonia (PCP), Aspergillus, candida
- Viral : Cytomegalovirus (CMV)
- Rare : Toxoplasma, strongyloides



The Most Common Opportunistic Infections in Renal Transplant Recipients

Peritransplant (<1 month)	Late (>6 months)
Wound infections	Aspergillus
Herpesvirus	Nocardia
Oral candidiasis	BK virus (polyoma)
Urinary tract infection	Herpes zoster
Early (1-6 months)	Hepatitis B
Pneumocystis carinii	Hepatitis C
Cytomegalovirus	
Legionella	
Listeria	
Hepatitis B	
Hepatitis C	

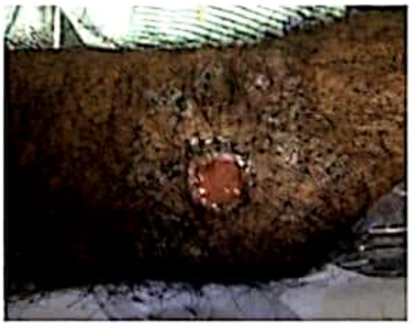
Infection in post HSCT : Infection
< 1 month : - Gram -ve pneumonia
- Aspergellosis (can be seen at anytime)

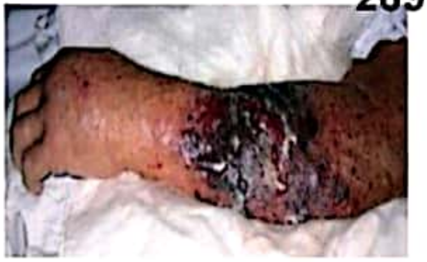
Opportunistic infections : (1- 4months)
- CMV
- PCP
- nocardia

- Acute onset of pneumonia within 24-48 hr mostly suggestive of Bacterial pneumonia
- Subacute onset of symptoms suggest - TB/Fungal /viral/Nocardiosis

Clinical assessment :

- minimally painful macules , papules or nodules → Fungal / nocardia





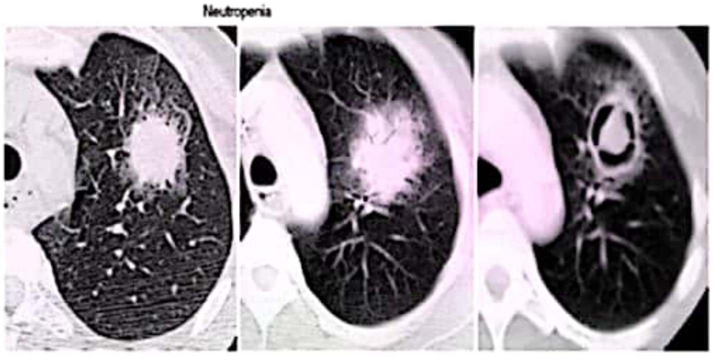
Ecthyma gangrenosum

- Ecthyma gangrenosum – pseudomonas
- Ocular examination – cmv
- organomegaly – TB /fungal
- Neurological examination – subacute / local brain abscess → Nocardia

Invasive aspergellosis

00:08:22

- mcc – A. fumigatus
- only seen in immunocompromised host → Neutropenia
- associated with Angioinvasion
- Clinical features – Fever with infiltrates – cavitation
- Conidia are aerosolized from invasive filaments called septate Hyphae
- Persistant Neutropenia is the single most important risk factor
- Hemorrhagic infarction due to the property of Angioinvasion



Halo sign D 0–5

Air space consolidation D 5–10

Air-crescent sign D 10–20

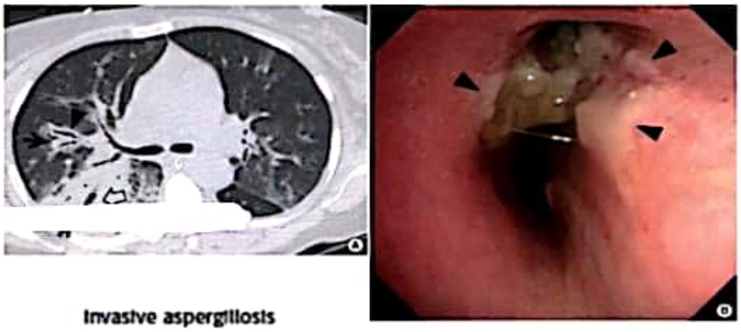
Evolution of radiography of invasive aspergillosis in an immunocompromised host. D = days after the lesion is first noted.

Halo sign :- Consolidation surrounded by ground glass opacification
- Seen very early
- Indicate acute infection

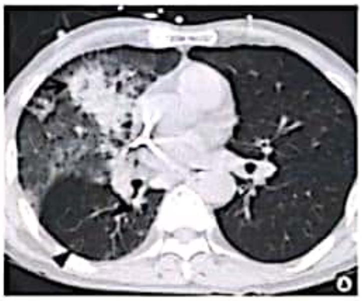
Air crescent sign : Sign of recovery .

Reverse Halo sign : Cryptogenic organism in ILD
monod sign : Fungal ball – Aspergilloma .

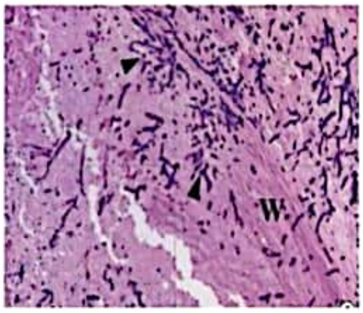
Extrapulmonary manifestation : CNS involvement has 100% mortality


Invasive aspergillosis

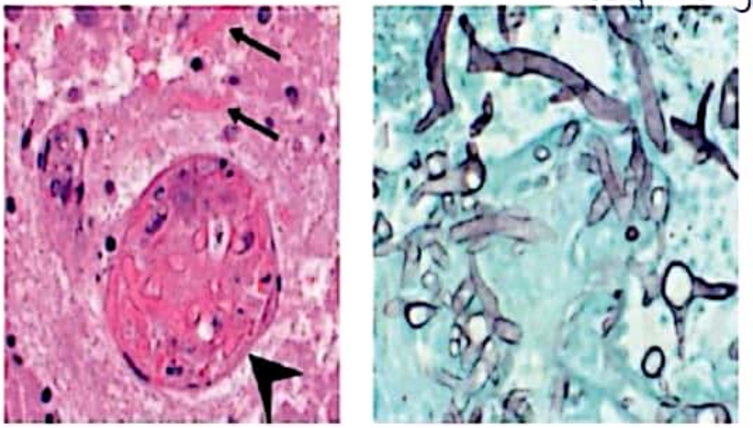
- Dense area of consolidation or diffuse thickening ⊕
- Bronchoscopy – Pseudomembrane in women


Candida aspiration pneumonia

Multifocal consolidation



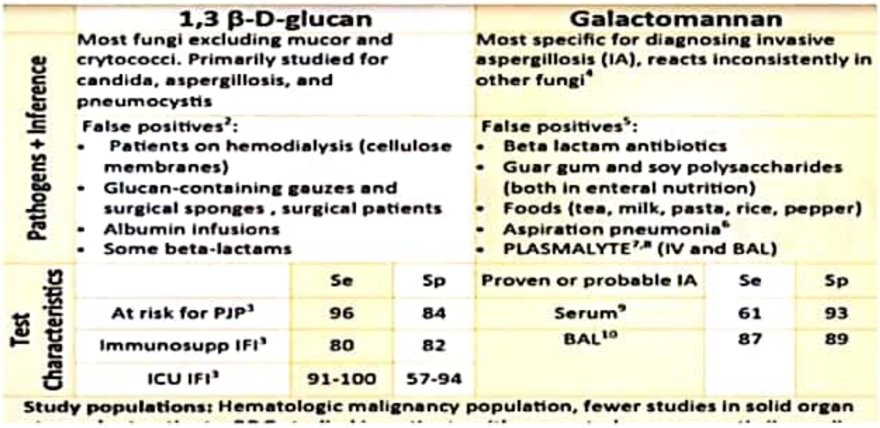
H&E → Aspergellus colenies
(Septate hyphal)



Aseptate Hyphae : Rhizopus or mucor

Diagnosis :

- Dichotomously branching septate hyphae on Bronchoalveolar lavage (BAL)
- Biopsy from nodule [Video Assisted thoracoscopic surgery]
- Galactomannan Test → 90% sensitivity & specificity
- 1. 3 β - D glucan Test → ⊕ for PCP, candida as well



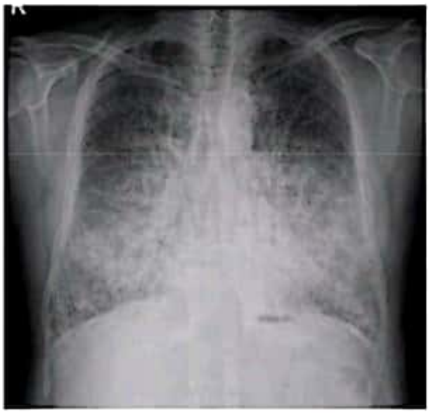
	1,3 β-D-glucan			Galactomannan		
Pathogens + Inference	Most fungi excluding mucor and crytococci. Primarily studied for candida, aspergillosis, and pneumocystis			Most specific for diagnosing invasive aspergillosis (IA), reacts inconsistently in other fungi[4]		
	False positives[2]: • Patients on hemodialysis (cellulose membranes) • Glucan-containing gauzes and surgical sponges , surgical patients • Albumin infusions • Some beta-lactams			False positives[5]: • Beta lactam antibiotics • Guar gum and soy polysaccharides (both in enteral nutrition) • Foods (tea, milk, pasta, rice, pepper) • Aspiration pneumonia[6] • PLASMALYTE[7,8] (IV and BAL)		
Test Characteristics		Se	Sp	Proven or probable IA	Se	Sp
	At risk for PJP[3]	96	84	Serum[9]	61	93
	Immunosupp IFI[3]	80	82	BAL[10]	87	89
	ICU IFI[3]	91-100	57-94			

Study populations: Hematologic malignancy population, fewer studies in solid organ

DOC Aspergellosis : Voriconazole

Other - Liposomal amphotericin B, Caspofungin

Mucormycosis :- Aseptate hyphal branching at right angle ,
- Persistently negative galactomann test
- Absence of response to voriconazole
- Managed by → Liposomal amphotericin B with posaconazole + surgical debridement of infected tissue



X-ray → No significant changes .

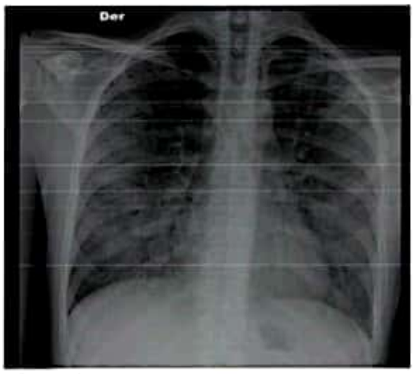
Pneumocystis jiroveci

00:17:52

- Clinical features : Fever, cough, tachypnea, tachycardia, bilateral perihilar infiltrate
  ↓
  Rapid hypoxia → Respiratory failure

- Opportunistic fungal pulmonary pathogen
  ↓ mc in
  HIV/AIDS (median CD_4 count is 300 cells /micro lts)

- β D glucan drive inflammatory response



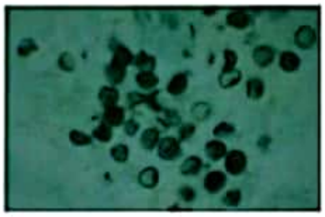
X - ray : Diffuse perihilar infiltrates (Non - specific)

LDH ↑ (> 400)
P_aO_2 ↓ (< 75)
+
Hypoxia
} PCP

- Lung findings Ⓝ (> 60% individual)

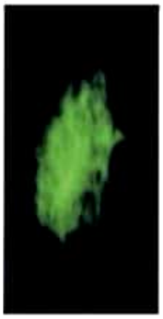
Microscopy : Gold standard [after BAL]

- Since *Pneumocystis* cannot be cultured, **the gold standard for diagnosis is microscopic visualization of the organism**.
- Traditionally different stains have been used to identify either the **trophic form** (Gram–Weigert, Wright–Giemsa or modified Papanicolaou stains) or the **cyst forms** (calcofluor white, cresyl violet, Gomori methenamine silver or toluidine blue)

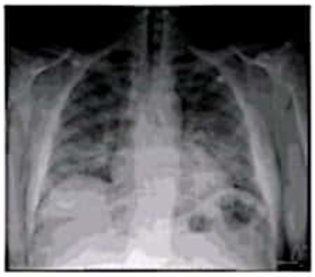


Methenamine silver stain of a bronchoalveolar lavage specimen showing a cluster of P. carinii cysts

Rapid test : Indirect immunofluorescence



Indirect immunofluorescence using monoclonal antibodies against *Pneumocystis jirovecii*

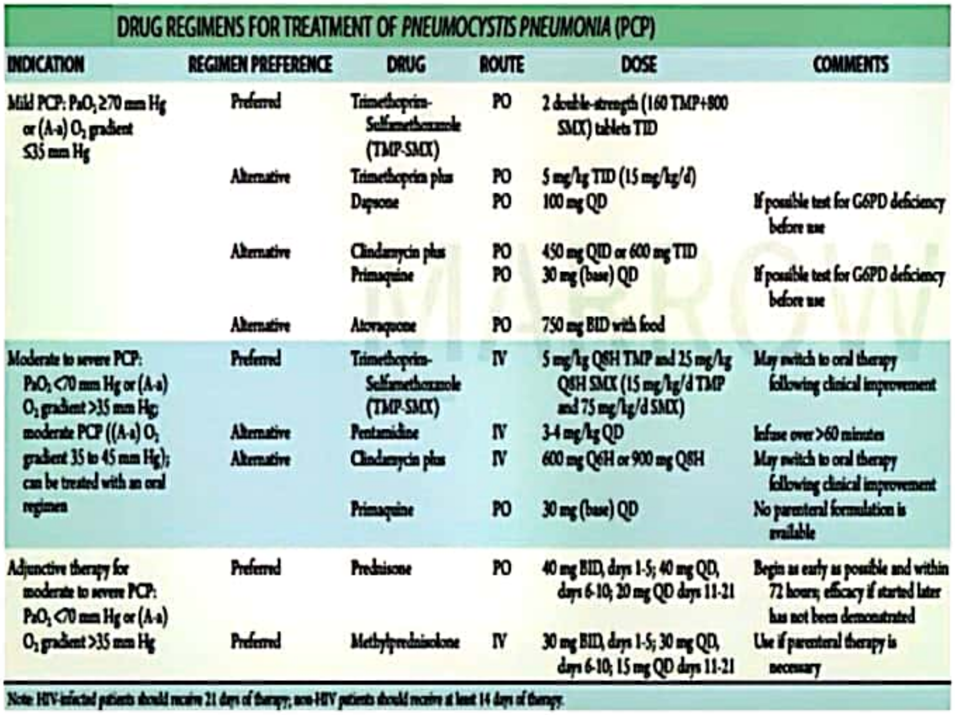


Chest radiograph demonstrating diffuse bilateral infiltrates in a patient with Pneumocystis jiroveci pneumonia

Complication : Pneumothorax (Ⓡ sided)
in PCP

Treatment : DOC – Cotrimoxazole Double strength → TDS + steroids

Trimethoprim (160mg) + sulfomethoxazole (800mg)



DRUG REGIMENS FOR TREATMENT OF *PNEUMOCYSTIS PNEUMONIA* (PCP)

INDICATION	REGIMEN PREFERENCE	DRUG	ROUTE	DOSE	COMMENTS
Mild PCP: $PaO_2 \geq 70$ mm Hg or (A-a) O_2 gradient ≤35 mm Hg	Preferred	Trimethoprim-Sulfamethoxazole (TMP-SMX)	PO	2 double-strength (160 TMP+800 SMX) tablets TID	
	Alternative	Trimethoprim plus	PO	5 mg/kg TID (15 mg/kg/d)	
		Dapsone	PO	100 mg QD	If possible test for G6PD deficiency before use
	Alternative	Clindamycin plus	PO	450 mg QID or 600 mg TID	
		Primaquine	PO	30 mg (base) QD	If possible test for G6PD deficiency before use
	Alternative	Atovaquone	PO	750 mg BID with food	
Moderate to severe PCP: $PaO_2 < 70$ mm Hg or (A-a) O_2 gradient >35 mm Hg; moderate PCP ((A-a) O_2 gradient 35 to 45 mm Hg); can be treated with an oral regimen	Preferred	Trimethoprim-Sulfamethoxazole (TMP-SMX)	IV	5 mg/kg Q8H TMP and 25 mg/kg Q8H SMX (15 mg/kg/d TMP and 75 mg/kg/d SMX)	May switch to oral therapy following clinical improvement
	Alternative	Pentamidine	IV	3-4 mg/kg QD	Infuse over >60 minutes
	Alternative	Clindamycin plus	IV	600 mg Q6H or 900 mg Q8H	May switch to oral therapy following clinical improvement
		Primaquine	PO	30 mg (base) QD	No parenteral formulation is available
Adjunctive therapy for moderate to severe PCP: $PaO_2 < 70$ mm Hg or (A-a) O_2 gradient >35 mm Hg	Preferred	Prednisone	PO	40 mg BID, days 1-5; 40 mg QD, days 6-10; 20 mg QD days 11-21	Begin as early as possible and within 72 hours; efficacy if started later has not been demonstrated
	Preferred	Methylprednisolone	IV	30 mg BID, days 1-5; 30 mg QD, days 6-10; 15 mg QD days 11-21	Use if parenteral therapy is necessary

Note: HIV-infected patients should receive 21 days of therapy; non-HIV patients should receive at least 14 days of therapy.

Prophylaxis :

- DOC : Cotrimoxazole → OD
- Alternatives : Dapsone (or) Dapsone + Pyrimethamine (or) pentamidine (or) Atovaquone

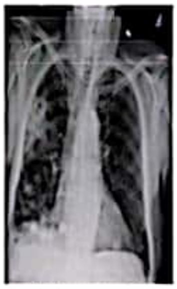
Nocardia asteroids

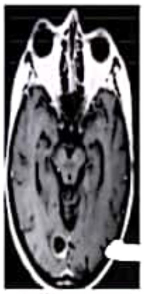
00:25:50

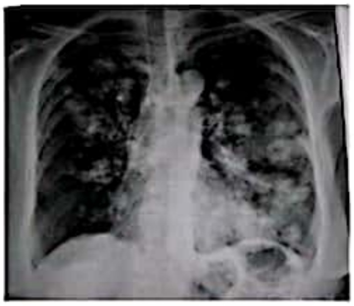
- Gram +, aerobic saprophyte, Actinomycetes
- Acquired by inhalation of fragmented mycelia
- Subacute presentation : Nodules infiltrating the lung

+

Sub acute brain abscess

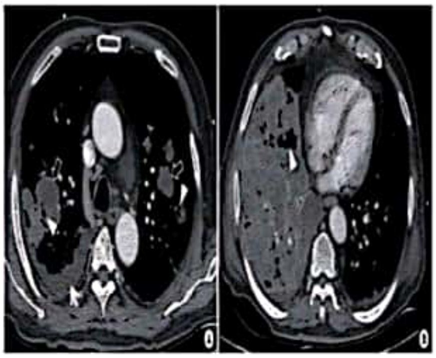




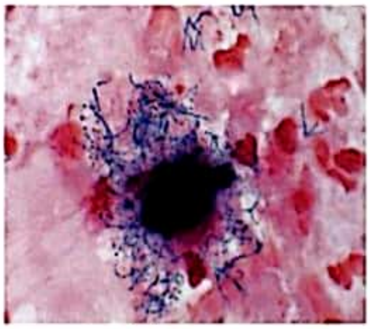


- X – ray :

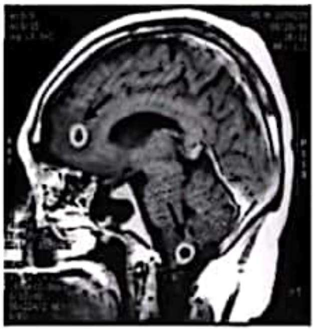
Dense bilateral infiltrates with cavitating Nodules



Multifocal Necrotic Consolidations



Gram-stained sputum



Brain Abscess

Sputum – Gram stain – Crooked branching beading filaments.
– Acid fast & paraffin baiting
– Slow growers on culture

Treatment : sulfonamides (DOC), minocycline
Imipenem/ Amikacin = established parenteral Drug.

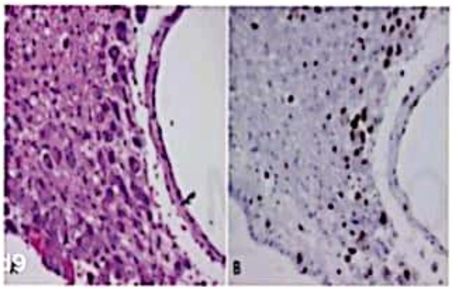
Subacute presentation : – cough, fever, sputum (thick)
– Hemoptysis → uncommon
– Extra pulmonary manifestations → common
→ mc = Brain

Nocardia	Actinomycetes
Saprophyte	anaerobe
aerobe	Natural inhabitant
acid fast	Non acid fast
exogenous	endogenous
impaired immunity	Normal immunity

Cytomegalo virus

- β – herpes DNA virus
- Presentation :– Subacute pneumonia
  - fever
  - leukopenia
  - fundus changes (pizza pie appearance)
  - GI symptoms

- CT → Bilateral Ground glass appearance
- CMV – DNA PCR → ↑
- Owl eye intranuclear inclusions
- DOC – IV Gancyclovir
- Other : CMV Hepatitis



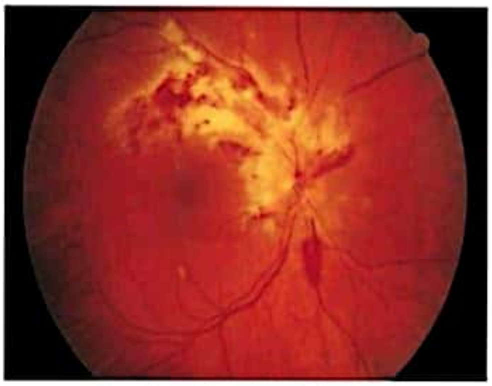
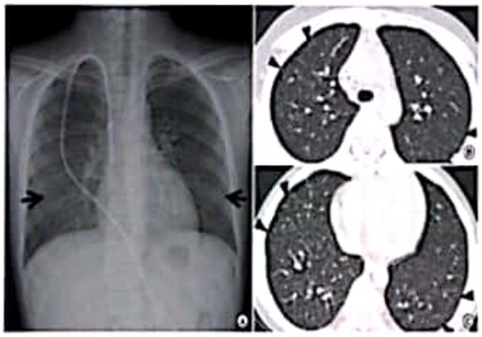


FIGURE 190-1 Cytomegalovirus infection in a patient with AIDS may appear as an arcuate zone of retinitis with hemorrhages and optic disk swelling. Often CMV



Cytomegalovirus pneumonia in a 14-year-old male who underwent allogenic hematopoietic stem cell transplantation 2 months ago. (A) Chest radiograph shows diffuse ill-defined ground glass opacities in both lower lung zones (arrows). (B, C) Lung window images of computed tomography scans (1.5-mm-section thickness) obtained at levels of aortic arch (B) and left ventricle (C), respectively, depict diffuse and poorly defined ground glass opacity nodules (arrowheads) in both lungs.

Active space

DEVELOPMENT OF RENAL SYSTEM

Development of urogenital system 00:01:56

- Develops from:
  - Intermediate mesoderm
  - Cloaca (Endodermal derivative)
    - → Rectum
    - Primitive urogenital sinus →
      - Bladder
      - Urethra

Intermediate mesoderm 00:04:05

- mesoderm is divided into:
  - Paraxial mesoderm → Somites
  - Lateral plate mesoderm → Pleura, peritoneum
  - Intermediate mesoderm

    ↓

    - Nephrogenic cord (urogenital ridge)
    - mesonephric duct (wolfian duct)
    - Paramesonephric duct (mullerian duct)
    - Gonads

Nephrogenic cord 00:07:24

- Extending from cervical to sacral region of embryo
- Aligned close to wolfian duct
- It is divided into:
  - Pronephros:
    - Develops by day 22
    - Regress by end of 4th week
  - mesonephros:
    - Develops by beginning of 5th week
    - Regress by 3-4 months
  - metanephros:
    - Adult kidney

Active space

Metanephros 00:11:00

- Formed by
  - mesenchyme of metanephric blastema → Excretory part
  - Epithelium of ureteric bud → Collecting part
- It is Epithelial mesenchymal interaction → 5 - 7th week
- First fully formed nephron → 8th week
- Ascent of Kidney with rotation → 9th week
- Fetal Kidney level → $S_1 - S_2$
- Adult Kidney → $T_{12} - L_3$
- Urine formation → 10th week

Epithelial mesenchymal interaction 00:16:24

- WT1 gene on chromosome 11
- PAX2 gene
- WT1 gene mutation causes:
  - WAGR syndrome:

    W → Wilms tumor
    A → Aniridia
    G → Genitourinary anomalies
    R → mental retardation
  - Denys Drash Syndrome:
    - Wilms tumor
    - Liver, Kidney, Spleen enlarged
    - male pseudohermaphroditism
    - Early onset renal failure
    - Diffuse mesangial sclerosis
- PAX2 gene mutation:
  - Renal hypoplasia
  - Optic nerve colobomas
  - Rarely unilateral renal agenesis

Beckwith wiedemann syndrome 00:20:05

- WT2 gene mutation
- microcephaly
- macroglossia

- Hemihypertrophy of testis
- Umbilical hernia
- Earlobe crease
- Wilms tumor

Microcephaly

Ear lobe crease

Macroglossia

Umbilical Hernia

Hemihypertrophy

RET/GDNF gene mutation

00:23:21

- RET gene produces → Glial derived neurotropic factor
- Mutation → B/L Renal agenesis

↓

Potters syndrome

↓

- B/L renal agenesis with absent renal arteries
- Lung Hypoplasia
- Disc shaped adrenals

- WNT4 and WNT6 genes → Tubular growth
- Nephrogenesis complete by 32–36 weeks
- Increase in concentrating capacity → 18 months
- Birth wt: 3 Kg → 9 lakhs nephrons
  1.5 Kg → < 2lakh nephrons

Active space

Collecting part of kidney 00:00:25

- It includes:
  - Connecting tubules
  - Collecting duct
  - Calyces
  - Pelvis
  - Ureter
- Urinary bladder arises from cloaca (endoderm)
  Except Trigone → mesoderm
- Urethra → Cloaca
  Except prostatic Urethra → mesoderm
- Renal Calyces:
  - 3 – 4 major calyces in each Kidney
  - 9 – 12 minor calyces in each Kidney

Renal pyramid 00:02:51

- Cone shaped structure
- Base → At corticomedullary junction
- Apex → Protrude into minor calyx
- Cortical tissue extending into the space between pyramid
  ↳ Columns of bertini
- Tip of pyramid → Papilla
- Renal papillary nercrosis → Hypoxia of papilla
  - Risk factors:
    - Complicated UTI
    - Diabetes mellitus
    - Sickle cell anaemia
    - Analgesic nerphropathy
- Vesicoureteric reflex: Loss of integrity of papilla
  ↳ Compound papilla (Upper Pole > Lower Pole > mid Zone)

IOC – micturationg cysto urethrogram (MCU)

- Simple pailla : Seen in normal individual
- Compound papilla : Promotes vesicoureteric reflex (VUR)
- Site- Upper pole > Lower pole > mid zone
- If MCU + for VUR : DMSA scan (Dimethyl mercapto Succinic Acid)- to look for scarring
- Asymmetric involvement of Kidney : . VUR
  RAS (Renal Artery Stenosis)
  Unilateral Renal agnesis / hypoplasia
- MCU scan done for - VUR , PUV(Posterior Urethral Valve)

Location and relationships of kidney 00:14:21

- $T_{12}-L_3$
- L_1 → Hilum
- Left Kidney at higher level
- Left renal vein is longer & crosses midline

$$\text{IVC} \xleftarrow{\text{Rt side}} \left\{\begin{array}{l} \bullet\ \text{Adrenal vein} \\ \bullet\ \text{Phrenic vein} \\ \bullet\ \text{Ureteral vein} \end{array}\right\} \xrightarrow{\text{Lt side}} \text{Left renal vein} \rightarrow \text{IVC}$$

- Aneurysm of Superior mesentric artery → Compress left renal vein
- Lt Renal Vein → Preferred for Transplant
- In Kidney transplant, Lt Renal Vein anastomosed to External liac vein
- Posterior relationship of Kidney formed by :
  - Psoas major
  - Quadratus lumborum
  - Transverse abdominis

Renal vasculature 00:18:48

- Renal artery is a lateral branch of abdominal aorta.
  Lateral branches of abdominal aorta-

1) Inferior phrenic artery
2) middle suprarenal artery
3) Renal artery
4) Gonadal artery

- Divides into segmental arteries

↙ ↘

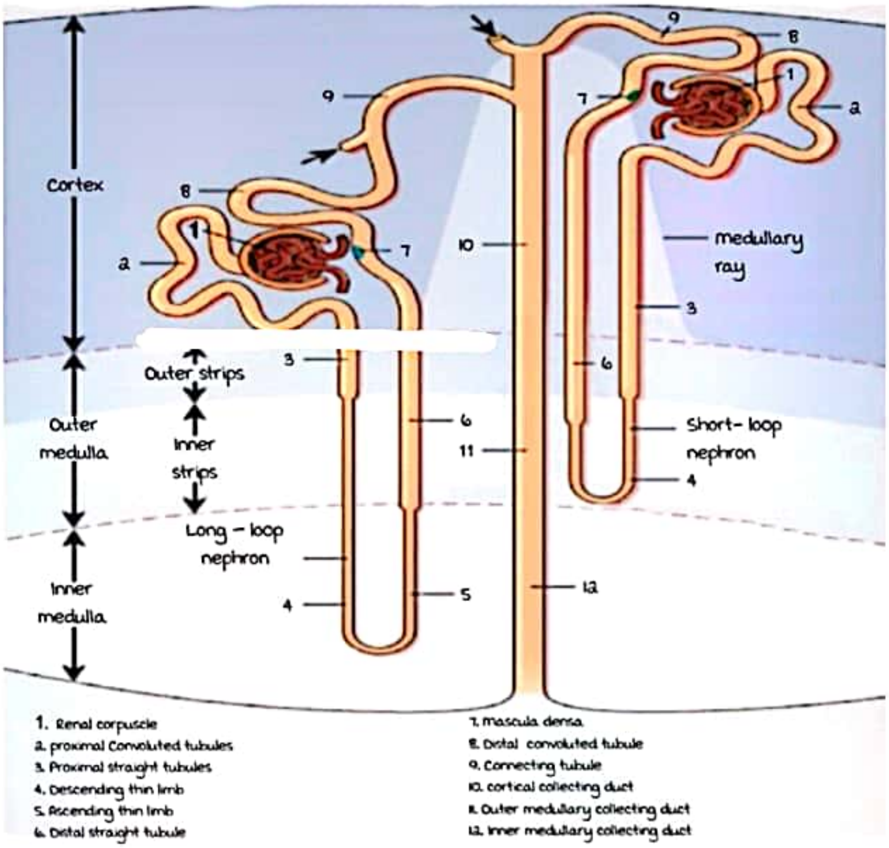
$$\underbrace{\text{4 Anterior segmental} \quad \text{1 Posterior segmental}}_{\text{large vessels}}$$

- $\text{Segmental A} \rightarrow \underbrace{\text{Interlobar Artery} \rightarrow \text{Arcuate Artery} \rightarrow \text{Interlobular Artery}}_{\text{Small vessels}}$
- Interlobular Artery → Afferent Arteriole → Glomerular Capillary Plexus → Efferent Arteriole ↓

IVC ← Renal vein ← limbs of vasa Recta ← Peritubular Capillary Plexus

Cortex vs medullary nephron

00:25:06


Cortex
Outer medulla
Inner medulla
Outer strips
Inner strips
Long-loop nephron
medullary ray
Short-loop nephron
1
2
3
4
5
6
7
8
9
10
11
12
1. Renal corpuscle
2. proximal Convoluted tubules
3. Proximal straight tubules
4. Descending thin limb
5. Ascending thin limb
6. Distal straight tubule
7. mascula densa
8. Distal convoluted tubule
9. Connecting tubule
10. cortical collecting duct
11. Outer medullary collecting duct
12. Inner medullary collecting duct

-Cortex - rich blood supply via Renal artery

-medulla - less blood supply - breaks down to peritubular capillary - vasarecta

The nephron is different in :

1) Cortex - short loop nephrons/ cortical nephrons (tip of loop of Henle is in junction of inner and outer medulla)

2) medulla - Long loop nephron / Juxtamedullary nephron (the tip of loop is present in inner medulla). Takes part in concentration of urine

Parts of a nephron 00:29:20

i) Glomerulus + Bowman's capsule = Renal corpuscle

ii) PCT (S_1, S_2 segment) (pars convoluta)

iii) Proximal straight tubule (S_3 segment) (Pars vecta) → Ischemia/ Hypoxia related tubular injury

- PCT + proximal traight tubule = Proximal tubule
  - function – reabsorption
  - Cuboidal epithelium
  - microvilli
  - ↑ mitochondria

iv) Thin descending limb of Henle loop

v) Thin ascending limb of Henle loop

Thin descending limb & ascending limb of henle loop = Intermediate tubule

vi) Thick ascending limb of Henle loop. (Distal straight tubule)

vii) Distal convulated tuble (DCT)

- Thick ascending limb of henle loop + DCT = Distal tubule

- Proximal tubule
  +
  Intermediate tubule
  +
  Distal tubule
  +
  Renal corpuscle

Excretory part of Kidney
↓
develops from mesenchyme of metanephrogenic blastema

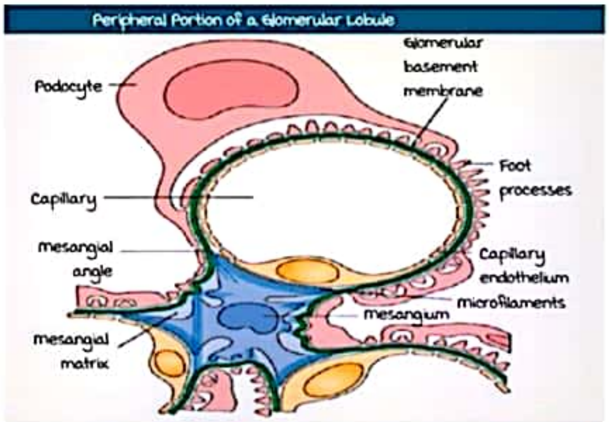
Warning: Not all points are covered in the notes, especially conceptual explanations. Please use the notes in conjunction with Marrow Edition 4 videos.

Macula densa & Juxtaglomerular apparatus 00:36:42

- Cortical portion of DST
- modified tall columnar cells
- Tubuloglomerular feedback
- macula densa

- Juxtaglomerular apparatus
- macula densa
- Function –tubulo glomerular feedback
- Juxta glomerular (JG) cells
- mesangial cells (Supporting Cells / Lacis Cells)
- Granular cells in the tunica media of afferent arteriole –Renin

Basic anatomy on nephron: Glomerulus 00:40:44


Peripheral Portion of a Glomerular Lobule
Podocyte
Glomerular basement membrane
Foot processes
Capillary
mesangial angle
Capillary endothelium
microfilaments
mesangium
mesangial matrix

Afferent arteriole → Glomerulus → Efferent arteriole

↓

Fenestrated Endothelial capillary loops (Endothelial capillaries with nucleus)

↓

Glomerular basement membrane (lining the capillary)

↓

Podocytes –present below GBM

↓

Attached to GBM with Foot Processes

↓

mesangial cells (supporting cells)

↓

mesangium contain Actin microfilaments

Microscopy: Staining 00:46:37

- H & E
- Periodic acid shiff
- Silver staining
- mason trichrome

} For Glomerular basement membrane study

Filtration 00:49:09

- Filtration barriers:
  - Fenestrated capillary endothelium
  - GBM
  - Filteration slit or slit diaphgram

- Size of the particles:
  - < 4 nm → Easily Filtered
  - > 8 nm → Never Filtered
  - 4–8 nm → Filtration depends on charge

- Capillary endothelium(filtration barrier)
  - Fenestrated (50 – 100 nm)
  - Strongly negative charged
    - ↳ ∵ of podocalyxin
  - Albumin →
    - Ⓝ 30mg / 24hrs in urine
    - Size: 7.6 nm
    - Negatively charged
    - Tubulotoxic

- microscopic hematuria →
  - Endothelial injury
  - Post Streptococcal glomerulonephritis

GBM 00:56:04

- Heparan sulphate proteoglycans → $\underbrace{\text{Perlecan and Agrin}}_{\text{Give negative charge}}$
- 350 – 400 nm
- Type IV collagen
- Collagen configuration:

$\alpha_1\,\alpha_1\,\alpha_2$ — Class switching → $\alpha_3\,\alpha_4\,\alpha_5$ (GBM, eyes, ears)

$\alpha_1\,\alpha_1\,\alpha_2$ — Class switching → $\alpha_5\,\alpha_5\,\alpha_6$ (Tubular BM, skin)

- Renal disease associated with GBM → Alports syndrome
  - ↓
  - microhematuria + Proteinuria

Podocyte filtration barrier 00:59:55

- Also called slit diaphgram/filtration slit
- major protein → Nephrin
- On podocyte major protein → Podocin
- 30–50 nm diameter
- Podocalyxin → Gives negative charge
- The Bowman's space is present between parietal epithelial cells and visceral epithelial cell (podocyte)
- In podocyte injury (podocytopathy)the basement membrane attaches to parietal epithelial cell forming synechiae & urine cannot pass into tubule but pass into tubulo interstium leading to tubular inflmmation →fibrosis → CKD.

↳ Severe proteinuria → medullary cystic disease, Focal segmental glomerulosclerosis, membranous nephropathy

Tubuloglomerular feedback 1:03:22

- Under the control of macula densa
- Cl^- and Na^+ load delivered to macula densa → High

↓

Release of adenosine

↓

Afferent arteriolar constriction

↓

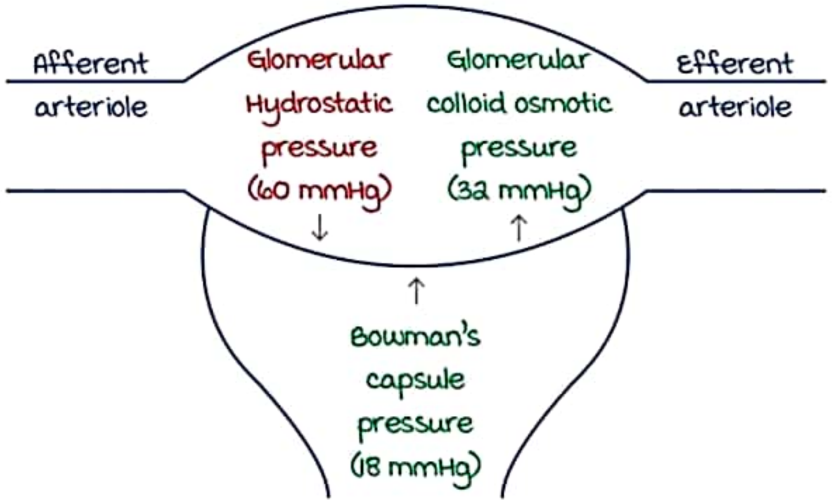
↓↓ GFR

Mesangial cells 1:09:27

- made of Actin microfilaments
- Injury → macrohematuria(contraction of action microfilaments vigorosly)
- Eg: IgA Nephropathy
- podocytes – terminally differentiated cells can't be replaced
- Differentiated podocytes can't replicate
- Kidney is divided into 6 compartments :
- I – Prerenal
- II – Large vessel: Renal artery and its branches
- III – Small vessels : Arcuate Inter lobar , inter lobular

PHYSIOLOGY OF RENAL SYSTEM

Pressure gradient 00:00:19


Afferent arteriole
Glomerular Hydrostatic pressure (60 mmHg) ↓
Glomerular colloid osmotic pressure (32 mmHg) ↑
Efferent arteriole
↑
Bowman's capsule pressure (18 mmHg)

- Net filtration pressure = Glomerular Hydrostatic pressure − Bowman's capsule pressure − Glomerular colloid osmotic pressure

  = 60 − 18 − 32

  = 10 mmHg

- GFR = Net ultrafiltration pressure x Ultrafiltration coefficient

  = 10 x 12.5

  = 125 ml/min

- Ultrafiltration coefficient = Depends on
  - Pore size
  - Permeability
  - Surface area

  = 12.5 ml/min/mm Hg

Active space

GFR & clearance 00:04:40

- For measurement of GFR substance should be:
  - Freely filtered
  - Not reabsorbed
  - Not secreted
- Gold standard → Inulin
- most sensitive & Specific → Tc EDTA clearance
- Bedside GFR estimation → Creatinine
- Clearance $= \frac{U \times V}{P}$ U – Urinary concentration
  P – Plasma concentration

$$= \frac{U_{creat}}{P_{creat}} \times \text{Flow rate (ml/min)}$$

- Creatinine → Undergoes tubular secretion
  ∴ Cr clearance = GFR + Tubular secretion
  ∴ Creatinine clearance always overestimates GFR
- Urea clearance = GFR – Tubular reabsorption
  ∴ Urea clearance underestimates GFR
- Creatinine clearance calculated by Cockroft and Gault equation

$$= \frac{(140 - \text{age}) \text{ Body wt}}{72 \times \text{S. creat}} \times 0.85\ (♀)$$

Pitfalls in using creatinine 00:17:09

- Fails to raise soon after injury (>24hrs), and is near normal in early CKD
- Sex
- muscle mass
- Cimetidine & Trimethoprim → ↑ S. creatinine
- Because of these pitfalls cystatin C can be used
- Cystatin C:
  - Produced by nucleated cells at constant rate
  - Elevated non specifically in inflammation / hypothyroid

Active space

Pitfalls of cockroft & Gault equation 00:21:09

- method of creatinine estimation → Jaffes method
- Creatine clearance ≠ GFR
- Body wt

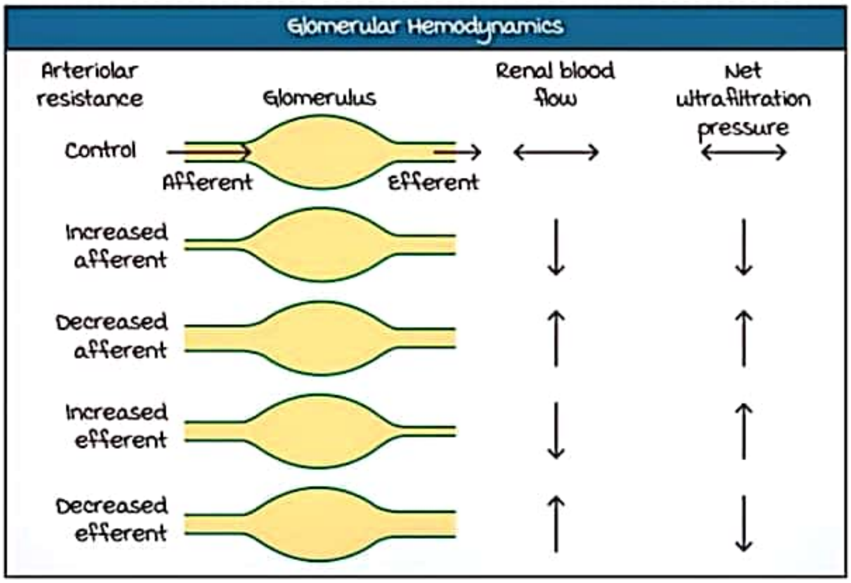
Currently used equation for GFR estimation 00:22:57

- Best method: CKD – EPI equation (Epidemiology problem initiative)
- MDRD equation (modification of Diet in Renal Disease)

- Advantages:
  - Standardized assays
  - GFR calculated directly
  - Weight replaced by Race

Renal autoregulation 00:25:36

- Autoregulatory range: 80 – 180 mmHg of mean Arterial Pressure
- Renal blood flow→ 1200 ml/min
- Renal blood flow → 700 ml/min
  - ↳ Estimation by para amino hippuric acid
- Renal autoregulation maintained by:
  - myogenic reflex (Stretch reflex)
  - Tubuloglomerular feedback (Adenosine)


Glomerular Hemodynamics
Arteriolar resistance
Glomerulus
Renal blood flow
Net ultrafiltration pressure
Control
Afferent
Efferent
↔
↔
Increased afferent
↓
↓
Decreased afferent
↑
↑
Increased efferent
↓
↑
Decreased efferent
↑
↓

Regulation	Mechanism	Effect on GFR
Histamine	Contraction of mesangial cells	↓
Dopamine	• Vasodilate • Decrease Renin and angiotensin II production • Relax mesangial cells	↑
Bradykinin	Release of NO and prostaglandin	↑
Prostaglandin	• Decrease vasoconstrictor effect of catecholamines and angiotensin II • Relax mesangial cells	↑
Nitirc oxide	Vasodilate afferent and efferent arteriole	↑
Endothelin	Vasoconstrict afferent and efferent arteriole	↓
Adenosine	Vasoconstrict afferent arteriole	↓

- Glomerulo tubular balance
  - Tubules ↑ the reabsorptive capacity in response to an ↑ in GFR, such that % of solute excreted will always be constant

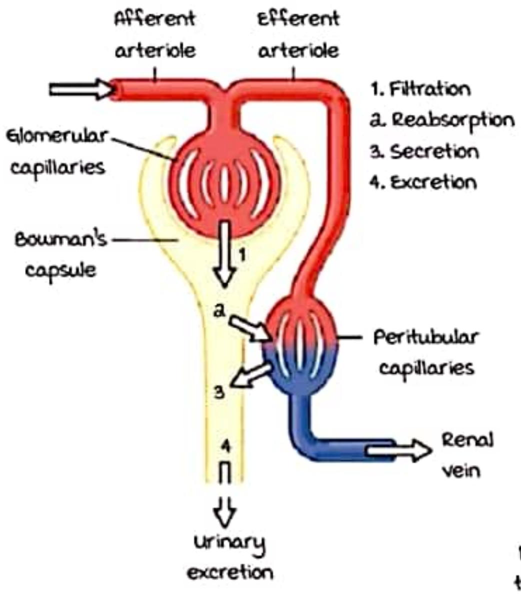
Filtration fraction

00:37:17

- Filtration fraction (FF) $= \frac{GFR}{RPF}$

$$= \frac{125}{700} = 0.1-0.2$$

Increased FF make elevated reabsorption of proximal tubule


Afferent arteriole
Efferent arteriole
Glomerular capillaries
Bowman's capsule
1. Filtration
2. Reabsorption
3. Secretion
4. Excretion
1
2
3
4
Peritubular capillaries
Renal vein
Urinary excretion

Increased FF

↓

The protein concentration in the plasma entering the peritubular capillaries increase

↓

The peritubular capillary oncotic pressure increases

↓

Enhancing fluid reabsorption from the renal interstitial space to the capillary

↓

Decreases renal interstitial pressure

↓

Favoring reabsorption across the tubular epithelium and minimizing back flux from the renal interstitial space to the tubule lumen

↓

↑ Reabsorption in proximal tubule

Countercurrent multiplication & exchange

00:40:30

- Countercurrent multiplication:
  - Osmolality of the fluid leaving the PCT is 285-290mOsm, the osmolality of fluid at the tip of loop of Henle is 1200mOsm
  - This increase from 290-1200 ⟹ Countercurrent multiplication
  - Occurs at descending limb of loop of Henle
- Countercurrent exchange:
  - ADH or vasopressin (V_2 receptor)
  - High medullary interstitial osmolality
  - Urea (reabsorbed from intermediate collecting ducts)
  - Vasa recta
- Furosemide → Na^+-K^+-$2Cl^-$ → Low medullary osmolality.
- Thiazide → Na^+ - Cl^- → medullary osmolality maintained

↓

ADH

↓

Hyponatremia

URINE ANALYSIS AND IMAGING

Introduction 00:00:50

- 3 investigations which should be upfront:
    - USG abdomen
    - Urine analysis
    - RFT

Ultrasound in kidney diseases 00:03:21

- Normal Kidney > 10 cm & corticomedullary differentiation maintained
- < 8 cm → contracted Kidney → CKD
- B/L Hydronephrosis/hydroureteronephrosis → post renal cause

Acute kidney injury 00:06:46

- Prerenal Prerenal - USG and Urine analysis - Normal
- Renal :
    - Vascular → Alb: Trace - 1 ⊕, HTN
    - Glomerular → Alb: 2+ - 3+, Hematuria
    - Tubulointerstitial → Albumin trace to 1+ , no HTN

Urine analysis 00:10:30

- Second morning midstream sample
- Analysis should be done within 3hrs
- Stored at 4-8°c → analysis within 12hrs

Colour of urine 00:11:17

- Rifampicin → Orange
- Desferrioxamine → Pink
- Imipenem → Darkening of urine on standing

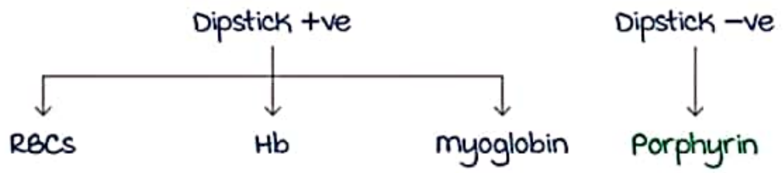
pH of urine 00:11:54

- First morning sample preferred
- Normal → 4–4.5 (Acidic)
- Early morning urine pH > 5.5 → Renal Tubular Acidosis

Specific gravity of urine 00:11:54

- Normal → 1.020 – 1.030.
- 1.010 → Kidney not concentrating urine.
  - → Isosthenuria → chronic tubulointestitial disease
- In AKI,
  - Specific gravity of 1.020 – 1.030 → Prerenal
    1.010 → Acute tubular injury

Blood in urine 00:20:05

It appears as
  - High coloured
  - Cola coloured
  - Blood
- Cause: 90% Urological
  9% Nephrological
  1% Hemolysis
- 

- Centrifuge at 1500 RPm for 5 minutes
- Still high coloured:
  - Hb
  - myoglobin (Has short t½ of 3 hrs)

40 – 5 – 1 rule

00:24:42

- RBCs(obtained after centrifugation)

↙ ↘

Non glomerular (urological) | Glomerular

- In order to be a glomerular pathology should
  40 – 5 – 1 rule
- 40% or more of dysmorphic RBC'S
  Or
- 5% or more Acanthocytes
  Or
- Single RBC cast
- microscopic hematuria : 3 or more RBC's per high power field after urine centrifugation

Proteinuria

00:27:45

- < 150 mg/24 hrs → Normal
- 150 – 500 mg/24 hrs → Functional proteinuria
- > 500 mg/24 hrs → Significant proteinuria
- > 3.5 gm/24 hrs → Nephrotic proteinuria → DM
- > 4 gm/24 hrs → massive proteinuria → Amyloidosis

- most important protein constituent in normal urine
  ↳
  - Tamm Horsfall Protein
  - Also called uromodulin
  - Thick ascending limb of loop of Henle

- < 30mg of albumin/24 hrs → Normal
- 30 – 300 mg of albumin/24 hrs → microalbuminuria
  - Endothelial damage
  - ↑ risk for CAD / Stroke
- > 300 mg albumin/24 hrs → Albuminuria
- > 2200 mg albumin/24 hrs → Nephrotic albuminuria

- Spot urine albumin creatinine ratio (ACR):
  - < 30 mg/g – Normal
  - 30 – 300 mg/g – Microalbuminuria
  - > 300 mg/g – Albuminuria
  - > 2200 mg/g – Nephrotic albuminuria

Dipstick test 00:34:30

- Pitfalls of dipstick testing
  - Qualitative test
  - Can't pickup minimal proteinuria
  - Can pickup only albumin
  - Overflow proteinuria : Loss of protein other than albumin, seen in multiple myeloma. Dipstick test is negative in this condition

Orthostatic proteinuria 00:37:42

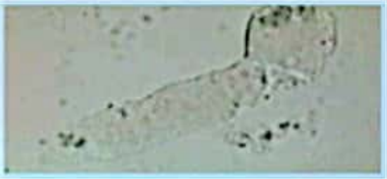
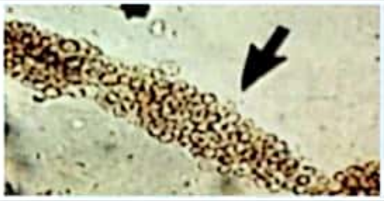
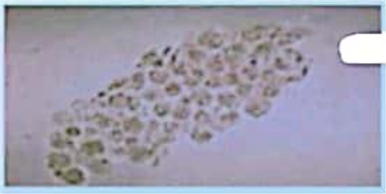
- Benign
- Diagnosis of exclusion
- < 1 gm/day
- As the day progresses → Proteinuria
- No Hematuria

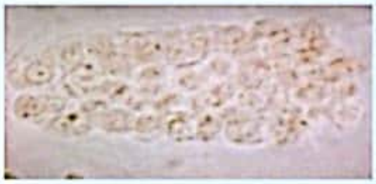
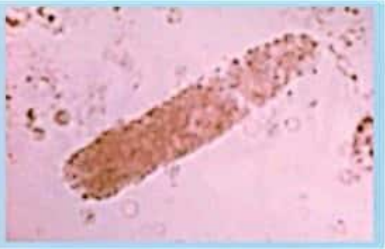
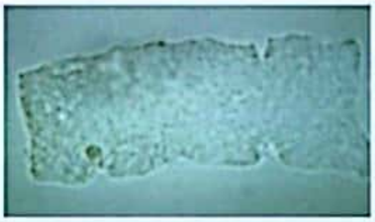
Selective proteinuria 00:39:00

- Only albumin & transferrin lost in urine
- It is seen only in MCD

Casts in urine 00:40:14

- Formed in DCT
- Matrix of cast → Tamm Horsfall protein
- Hyaline cast – Insignificant
- Fine granular cast – Represents Kidney injury but cannot localise
- Pigmented granular cast – Rhabdomyolysis, Hemolysis
- Waxy cast – Suggestive of Chronic Kidney Disease or IFTA (Interstitial Fibrosis Tubular Atrophy)
- Renal Tubular cast – Acute tubulointerstitial nephritis -->
  - muddy brown renal tubular epithelial cast (most specific)
  - Eosinophil cast
  - WBC cast
- RBC cast – Glomerular hematuria – IgA nephropathy

Hyaline cast	Colorless and homogenous	
RBC cast	Orange red to brown	
WBC cast	Indicate inflammation with RBC cast indicate glomerulonephritis	

Renal tubular cast	Large size, cell arranged in parallel rows	
Granular cast	Increase in urine after strenuous exercise	
Waxy cast	Strenuous looking with blunt end and serrated marging show in renal failure	

- Fractured cast seen in myeloma, the only cast which cannot be seen in urine

Crystals in urine

00:47:13

- Rhomboid shape → Uric acid crystals
- Envelope shape → Calcium oxalate dihydrate
- Dumbbell shape → Calcium oxalate monohydrate
- Star shape → Calcium phosphate

- Coffin lid shape → Struvite (triple phosphate)
- Hexagonal → Cystine crystals
- Broom brush → Amoxicillin
- Fatty casts on polarized microscope → Oval fat bodies / maltese cross deposits
- maltese cross deposits:
  - In urine → Fabry's disease
  - In Blood → Babesiosis

DMSA and DTPA scans

00:51:07

- DMSA Scan:
  - Assess degree of scarring, size, shape
- DTPA Scan:
  - Assess individual Kidney GFR

If renal failure present → DTPA scan is contraindicated → MAG-3 scan is preferred

Active space

VASCULAR DISEASES OF KIDNEY

Introduction 00:00:15

- Large vessel diseases:
  - Renal artery stenosis
  - Renovascular HTN
  - Renal artery occlusive disease
- Small vessel disease:
  - Thrombotic microangiopathy

Large vessel diseases: RAS 00:01:41

- RAS: Renal artery stenosis
  - Ischaemic nephropathy
  - mc cause → Atherosclerosis
  - RAS in young →
    - India → Takayasu arteritis
    - World → Fibromuscular dysplasia (F : M = 9 : 1)
- RAS in young male → Polyarteritis nodosa
  - ↳ Renal artery microaneurysms

Fibromuscular dysplasia 00:04:55

- Young females
- 25 yrs
- mid to distal renal artery involvement
- 25% → Cerebral vessels
- 10% → marfans / Ehler danlos
- CT renal angiogram: String of Beads
- Treatment:
  - Percutaneous transluminal renal angioplasty

Atherosclerotic RAS 00:09:32

- Unilateral RAS:
  - 70 – 80% occlusion → Fall in renal perfusion pressure
  - Characterised by ↑ BP
  - It is pressure dependent HTN

- Features:
    - Uncontrolled HTN
    - Elderly HTN
    - Asymmetrical Kidneys (> 1.5cm)
    - RFT- Ⓝ
    - Edema absent
- Doc: ACE ⊖
- Bilateral RAS:
    - Volume dependent HTN
    - Symptoms:
        - Flash pulmonary edema
        - Renal failure after ACE ⊖
        - Renal failure ⊕
        - Edema absent. (∵ ↑ intravascular volume)
        - Evidence of Atherosclerosis elsewhere
        - H/O Smoking, POVD Peripheral Occlusive Vascular Disease
        - Femoral /Renal / Abdominal bruit
- Doc: Diuretics

Goldblatt kidney model 00:20:41

- U/L RAS → 2 Kidney 1 clip model
- B/L RAS → 2 Kidney 2 clip model

Evaluation of RAS 00:21:36

- Screening:
    - Renal artery doppler with USG
    - ↓ Resistivity Index
    - ↑ Peak systolic velocity > 250cm/s (most sensitive)

    } Direct criteria

    - Parvus tardus
    - Prolonged acceleration time
    - Absence of extra systolic peaking (most sensitive)

    } Indirect criteria

- Ioc: CT Renal angiography / MR angiogram

Treatment of RAS 00:25:09

- Unilateral RAS:
  - Percutaneous Transluminal Angioplasty (PTRA) with stenting of affected side
  - ACE inhibitors
  - Intervention depends on:
    - Size of the kidney
    - Lateralization tests:
      - Captopril renogram
      - Renal vein rennin levels
- Bilateral RAS:
  - medical management is superior
  - Stop smoking, Statins, Diuretics
  - For flash pulmonary edema: PTRA + Stenting

Small vessel disease (thrombotic microangiopathies) 00:28:54

- HUS
- Malignant HTN
- Preeclampsia (HELLP syndrome)
- APLA syndrome
- Scleroderma renal crisis

Malignant hypertension 00:34:41

- HTN emergency + papilledema
- Fibrinoid necrosis
- Flea bitten kidney
- Hyperplastic arteriosclerosis

Hemolytic uremic syndrome (HUS) 00:35:25

- Endothelial injury → Release of vWF

  ↓

  Subendothelial collagen

  ↓

  Platelet plug formation

- Thrombocytopenia
- microangiopathic Hemolytic anemia → schistocytes or fragmented RBC's
- Renal failure
- Types of HUS:
  - Childhood HUS (Typical/D^+ HUS)
  - Triggering factors :
  - Diarrhoea / Dysentry – 90%
  - Pneumonia – 10%
    - Organisms:
      - EEHEC → O157:H7 (SLT or VCT toxins) – most common
      - Shigelia dysentriae (Shigatoxin)
      - Strep. pneumonia(Neuraminidase)
    - After 1–4 WKS of infection → HUS
    - 5% risk for HUS
    - Treatment
      - Conservative treatment
      - No role for Antibiotics
      - 100% Recovery

Warning : Not all points are covered in the notes, especially conceptual explanations. Please use the notes in conjunction with Marrow Edition 4 videos.

- Adult HUS (Atypical HUS/D^- HUS)
  - Genetic
  - Sporadic

Genetic	Sporadic
• Under Genetic heading	• Drugs
• Complement factor H mutation (mc)	• HIV
• MCP mutation (Best prognosis)	• SLE
• Complement factor I.	• Pregnancy
• Complement factor B. (worst prognosis)	• Post bone marrow transplant

- Normally Factor H,I,B, membrane Cofactor Protein (MCP) → Inhibit the activation of C3 nephritic factor.
- Mutation of factors H,I,B,MCP → uncontrolled activation of C3 nephritic factor
- C3 – Low
- C4 – normal

- Treatment
  - Plasmapheresis within 24hrs
  - Factor H mutation – Steroids
- Post transplant recurrence Rx:
  - Rituximab (Anti CD20)
  - Eculizumab (Anti C_5)
  - High recurrence even after transplant

- Drug induced HUS :
- Mitomycin (in red)
- Cisplatin
- Gemcitabine
- Tacrolimus
- Cyclosporine
- Ticlopidine
- Clopidogrel

MCD, FSGS

Presentation of glomerular diseases 00:01:05

- Asymptomatic
- macrohematuria
- Nephrotic syndrome
- Nephritic syndrome
- RPGN
- Chronic glomerulonephritis

Asymptomatic presentation 00:02:38

- Asymptomatic →
    - Proteinuria
    - microscopic hematuria
- On renal biopsy
    - FSGS
    - membranous nephropathy
    - IgA nephropathy

Macrohematuria 00:04:59

- Should satisfy 40/5/1 rule
- Glomerular hematuria is an absolute indication for renal biopsy
- On Biopsy → Ig A nephropathy

Nephrotic syndrome(NS) 00:05:48

- mcc in
    - children → MCD(minimal change disease)
    - Adult → FSGS
    - Elderly (> 60 yr) → membranous nephropathy
- Nephrotic proteinuria
    - > 3.5 gm/24 hrs
    - > 2.2 gm albumin / 24 hrs

      Or
    - >50 mg /kg/day
    - > 4 mg/kg/hr

- Hypoalbuminemia
- Edema
- Hyperlipidemia(extravascular)
- Lipiduria

Reasons for clinical presentations of nephrotic syndrome

00:11:13

- Hypoalbuminemia:
  - Due to:
    - Loss of albumin in urine
    - Blunted compensation by liver
  - Muehrcke's lines over nails
  - Loss of muscle proteins, Amino acids
- Edema:
  - Underfill theory → Extravascular loss of oncotic pressure
  - Overfill theory (10%) → Defective tubular excretion
    - ↳ Na^+ and H_2O retention
- Hyperlipidemia:
  - Loss of HDL in urine
  - ↑ VLDL synthesis by liver
  - ↓ Lipoprotein lipase (↑ TG)
  - ↓ LCAT(Lecithin cholesterol acyl transferase)
  - Total cholesterol ↑
  - LDL is normal
- Lipiduria:
  - Oval fat bodies
    - ↳ Under polarized microscope → Maltese cross deposit

Complications of nephrotic syndrome

00:17:56

- Thrombosis:
  - Renal vein thrombosis
  - DVT
  - It occurs due to:
    - Loss of Antithrombin III in Urine
    - Loss of protein C & S
    - ↑ Fibrinogen

  - ↑ Platelet aggregation
  - ↓ Plasminogen

- Renal vein thrombosis:
  - mcc in
    - Child → Dehydration
    - Adult → membranous glomerulonephritis
    - Elderly → RCC
  - Abdominal pain + Hematuria
  - IOC: CECT
  - Treatment: Anticoagulants

- Peritonitis:
  - Pneumococcal
  - mcc of death in nephrotic syndrome

Glomerular proteinuria	vs	Tubular proteinemia
↓		↓
main protein lost:albumin (2+ or 3+)		beta 2 glycoprotein>albumin(trace or 1+)

- Vit D binding globulin & thyroxin binding globulin lost in urine
- Clofibrate toxicity → Rhabdomyolysis
- Salt restriction < 2 gm/day
- Protein → 0.8 – 1 gm /Kg/day
- Target BP → 130 / 80 mmHg

Nephritic syndrome / Acute glomerular nephritis 00:28:24

- Acute
- Cola coloured urine
- Deranged RFT
- minimal edema
- Hypertension
- Pulmonary edema
- PSGN presents as AGN
- MPGN → Nephrotic / Nephritic syndrome

[redacted] **Differentiation Between Nephrotic Syndrome and Nephritic Syndrome**

Typical Features	Nephrotic	Nephritic
Onset	Insidious	Abrupt
Edema	++++	++
Blood pressure	Normal	Raised
Jugular venous pressure	Normal/low	Raised
Proteinuria	++++	++
Hematuria	may / may not occur	+++
Red cell casts	Absent	Present
Serum albumin	Low	Normal / Slightly reduced

RPGN

00:32:10

- Rapidly progressive glomerulonephritis
- Rapidly progressive renal failure
- Days – weeks
- Acute deterioration of renal function with crescentic nephritis
- Pedal edema
- Facial puffiness
- High coloured urine
- ↓↓ urine output
- HTN
- uremia
- Hemodialysis should be done before biopsy to prevent uremic bleeding
- Biopsy findings:
  - Crescents
  - Collapse of glomeruli
  - Parietal epithelial cell proliferation along with fibrin & platelets

Active space

Types of RPGN

00:43:38

- Good pasture syndrome: (Type I)
  - Linear IgG deposits
  - Along the capillary wall & GBM
  - Ribbon shaped

- Immune complex mediated (Type 2)
  - Granular IgG + C_3 deposits
  - Subepithelial deposits
  - Ex: • IGA HSP
    - SLE
    - Post-infectious glomerulonephritis (PIGN)

- Pauci immune (No Immune complex deposition) (Type 3)
  - Wegeners
  - microscopic polyangitis
  - Churg strauss syndrome

- Double positive type 4 (Anti GBM + ANCA)

- Double negative type 5 (Anti GBM + ANCA negative)

- In all ages → Type III is mc
- 1 – 20yrs → Type II is mc
- 21 – 60yrs → Type III is mc
- > 60yrs → Type III is mc

Podocytopathies

00:50:14

- mCD
- FSGS
- mN

- Effacement or loss of foot process of podocytes
  ↳ ∴ protein can easily pass through
  ↓
  Proteinuria

MCD (lipoid nephrosis) 00:51:29

- 2 – 7yr old children
- 90% of childhood nephrotic syndrome → MCD
- 10 – 15% of adult NS → MCD
- No risk of progression to CKD
- 100% MCD patients come with → Nephrotic syndrome

- Secondary causes of MCD :
    - Drugs: NSAID'S, IFN-α
    - Allergy → Allergic rhinitis
    - Post immunization
    - Hodgkins disease

- microscopy findings:
    - Light microscopy } Normal
    - Immunoflurescence } Normal
    - Ig m positive → Ig m nephropathy
    - Electron microscopy → Effacement of foot process of podocyte

Management of MCD 01:01:13

Treatment with steroids

↓ 95% Steroid responders

↓

Child:- 60 mg/m²/day x 6 weeks, taper & stop over another 6 weeks

Adult:- 1 mg/kg/day

↓ 5% Steroid resistant

↓

Proteinuria persisting despite full dose steroids for 4 wks in child, 4 months in adult

↓

- DOC → Calcineurin inhibitors
    - Tacrolimus / cyclosporine
    - Levamisole

- Remission: Urine routine examination Nil for 3 consecutive days.
- Relapse:
    - 2nd attack after minimum 4 weeks of remission

    - Taper from day of response and stop over 4 weeks
  - 2 + relapses in 6 months → Frequent relapse

- Steroid dependence:
  - Relapses ≥ 2 while on alternate day dose, or within 14 days of stopping steroid
  - Treatment:
    - Doc → Cyclophosphamide
    - Levamisole
    - Rituximab

FSGS 01:11:50

- Focal segmental glomerulosclerosis
- < 50% glomeruli involvement
- Segmental involvement

Secondary FSGS 01:13:35

- 2° FSGS → Nephrotic proteinuria
- Causes:
  - Drugs →
    - IFN α
    - Heroin
    - Pamidronate
    - Sirolimus
  - Infection →
    - HIV
    - Parvo virus B19
    - EBV/CMV
  - Cyanotic congenital heart disease
  - Obesity
  - Sickle cell anemia
  - Anabolic steroids

- Perihilar 2° FSGS:
  - Secondary to decrease in nephron number
  - Hyperfiltration injury
  - FSGS due to adaptive response

Clinical presentation of FSGS

01:17:35

- 75% → Nephrotic syndrome
- 25% → Asymptomatic
- HTN
- microhematuria
- Renal failure

Primary FSGS

01:20:37

- Due to circulating permeability factor
  ↳ SUPAR
  (Soluble Urokinase Plasminogen Activator Receptor)
- 50% develop CKD by 10 yrs
- Types of FSGS:
  - Tip variant → Best prognosis
  - Classical FSGS → mc type
  - Cellular
  - Perihilar
  - Collapsing → worst prognosis

Microscopic findings in FSGS

01:22:46

- Immunoflurоscence:
  - 1° FSGS → Focal Igm + C_3
  - 2° FSGS → IF negative
- Electron microscopy:
  - Diffuse effacement of foot process of podocyte

Collapsing FSGS

01:24:07

- Causes:
  - HIV
  - Heroin
  - Pamidronate
  - Parvo B19
  - IFN α
- Worst prognosis
- Collapse of glomeruli with hypertrophy of podocytes

- Pseudo crescents: Podocyte with protein droplets
- Dilated tubules & microcyst

Treatment of FSGS 01:26:52

- Asymptomatic patients:
  - BP control
  - ACE ⊖
  - Avoid high protein diet
  - Better prognosis
- Nephrotic syndrome patients:
  - Steroids for 6 months
  - In steroid resistance →
    - Cyclosporine (DOC)
    - Cyclophosphamide
    - Galactose

Steroid resistant FSGS in children 01:28:45

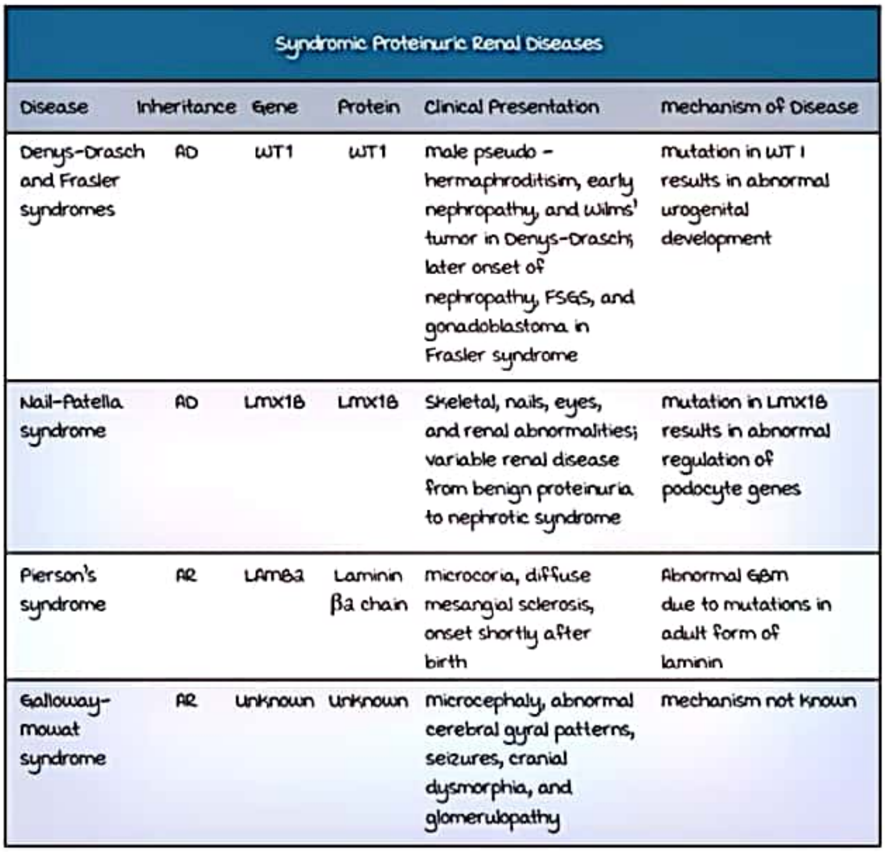
- Autosomal dominant:
  - α Actinin 4 → FSGS type I → 20–30 yrs, Better prognosis
  - $TRPC_6$ (Transient receptor potential channel 6)
    - → FSGS type II → Adolescents
- Autosomal recessive:
  - Podocin mutation
  - $NPHS_2$ gene on chromosome 1 → Podocin
  - Steroid resistant nephrotic syndrome under 3 yr age
  - Progresses to end stage renal disease by 10 – 15 yrs of age

Congenital nephrotic syndrome 01:32:10

- $NPHS_1$ gene on chromosome 19 → Nephrin
- Autosomal recessive
- Nephrotic syndrome at birth
- 100% mortality
- Premature baby
- massive edema
- Large placenta
- On light microscopy: Diffuse mesangial sclerosis
- No response to any drugs

MN, MPGN

Syndromic proteinuric renal diseases 00:00:14



Syndromic Proteinuric Renal Diseases

Disease	Inheritance	Gene	Protein	Clinical Presentation	Mechanism of Disease
Denys-Drasch and Frasier syndromes	AD	WT1	WT1	male pseudo - hermaphroditisim, early nephropathy, and Wilms' tumor in Denys-Drasch; later onset of nephropathy, FSGS, and gonadoblastoma in Frasier syndrome	mutation in WT 1 results in abnormal urogenital development
Nail-Patella syndrome	AD	LMX1B	LMX1B	Skeletal, nails, eyes, and renal abnormalities; variable renal disease from benign proteinuria to nephrotic syndrome	mutation in LMX1B results in abnormal regulation of podocyte genes
Pierson's syndrome	AR	LAMB2	Laminin β2 chain	microcoria, diffuse mesangial sclerosis, onset shortly after birth	Abnormal GBM due to mutations in adult form of laminin
Galloway-mowat syndrome	AR	unknown	unknown	microcephaly, abnormal cerebral gyral patterns, seizures, cranial dysmorphia, and glomerulopathy	mechanism not known

Membranous nephropathy 00:02:01

- Primary membranous nephropathy:
  - Antibody against Phospholipase A_2 receptors (Anti PLA_2R)
  - 85% of primary MN → Anti PLA_2R ⊕
  - Bad prognosis
- Secondary MN:
  - Drugs →
    - Captopril
    - Gold
    - D - Penicillamine
    - mercury
    - NSAIDS
- Infections →
  - Hepatitis B

Active space

- Autoimmune →
  - SLE
  - RA
  - Hashimotos thyroiditis
  - Graves disease
  - Sarcoidosis
- Secondary to malignancy:
  - Adenocarcinoma colo-rectal / Stomach / Lung / Prostate

- Heymann Rat model: Initial model for membranous nephropathy

Clinical presentation of MN 00:07:48

- 70% → Nephrotic syndrome
- 30% → Asymptomatic
- MN vs MCD →
  - microhematuria
  - HTN
  - Renal failure
- MN vs FSGS →
  - Thrombosis
    - ↳ Limb arteries / Renal vein thrombosis

Microscopy findings 00:09:50

- Light microscopy:
  - Uniform thickening of GBM
  - Swiss cheese appearances
- Immunofluorescence:
  - Granular IgG ± C_3 in the capillary wall
- Electron microscopy:
  - Subepithelial depositis
  - Basement membrane projecting between deposits
    - ↳ Spikes

Treatment of MN 00:14:02

- Non Immunosuppressive therapy:
  - ACE inhibitors
  - BP → 130/80 mmHg
  - Statins
  - Anticoagulants
  - Avoid high protein diet
- ⅓ Rule:
  - ⅓ cases → Spontaneous remission
  - ⅓ cases → Heavy proteinuria but normal kidney function
  - ⅓ cases → Develops end stage renal disease.
- Immunosupressive therapy:
  - Ponticelli regimen:
    - Alternating doses of steroids & Oral cyclophosphamide for 6 months
  - Rituximab
  - Calcineurin inhibitors

Prognostic factors: 00:18:34

- Good
  - Female sex
  - 30% asymptomatic patients with microhematuria & proteinuria
- Bad:
  - Anti PLA$_2$R

Membranoproliferative glomerulonephritis (MPGN) 00:19:29

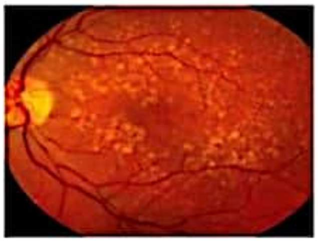
- Also called mesangiocapillary GN
- It is almost always 2°
- Infections:
  - HCV
  - Leprosy
  - Schistosomiasis
  - All parasitic infections-mesangioproliferative gene
  - malaria- DPGN
  - P. malariae - MPGN
- malignancy:
  - Plasma cell disorders
  - CLL

Active space

- Autoimmune:
    - SLE
    - Scleroderma (mc Kidney involvement : small vessel ; mc glomerular involvement : MPGN)
    - Sjogrens syndrome (mc Kidney involvement : chronic tubulointestinal ; mc glomerular involvement : MPGN)
- Cryoglobulinemia
- Infective endocarditis
- Shunt infections

Clinical presentation of MPGN

00:25:39



- 35% cases → Nephrotic syndrome
- 35% cases → Nephritic syndrome
- 20% cases → RPGN Type II
- 10% cases → CKD
- High recurrence in post transplant patients
- Classical MPGN :old type I MPGN
- Acquired partial lipodystrophy of face
- Retinal Drusen

} Old Type 2MPGN / C_3GN

Microscopy findings

00:28:40

- Light microscopy:
    - Endocapillary hypercellularity
    - Mesangial Hypercellularity
    - Lobular appearance of capillary tuft
    - Small uniform nodules
    - Mild thickening of glomerular BM
- Immunoflurescence:
    - MPGN (classical) → Granular IgG + IgM ± C_3 in the capillary wall and mesangium
    - C_3GN → Granular C_3 ± IgG in mesangium & capillary wall
- Electron microscopy:
    - Classical MPGN:
        - Subendothelial deposits IgG ± IgM ± C_3
        - Double contour / Tram track appearance
    - C_3GN: Intramembranous dense deposits of C_3 ± IgG
      ∴ Called Dense deposit disease
    - C_3GN → 100% risk for recurrence post transplant

IGA NEPHROPATHY, PSGN

IgA nephropathy 00:00:10

- Also called Henoch schonlein nephritis / IgA vasculitis / Buerger's disease
- MC glomerular disease
- Types:
  - Monomeric IgA →produced from bone marrow
  - Polymeric IgA → pIgA₁
    - ↳ Predominantly from mucosa associated lymphoid tissue(MALT)
- Generally, the increased polymeric Ig A is cleared by the liver in normal individuals.
- In Ig A nephropathy- Polymeric IgA is Galactose deficient

↓

Not cleared by Liver

↓

Antiglycan Ab's against pIgA₁

↓

Immune complexes formation

↓

deposited in mesangium
(Innocent bystander mechanism)

Secondary causes of IgA nephropathy 00:05:13

- Mucosal diseases →
  - Celiac disease
  - Dermatitis herpetiformis
  - Crohn's disease
  - Ulcerative colitis
- Chronic liver disease → Alcohol
- Seronegative spondyloarthropathies (RF negative)

Active space

Primary IgA nephropathy 00:07:10

- >50% patients → Sympharyngitic episodic macrohematuria with intervening microhematuria and proteinuria

- 30 – 40% patients → Asymptomatic microhematuria & proteinuria
- 10% patients → CKD – CGN
- 5% patients → Nephrotic syndrome
- 1% patients → RPGN type 2 – in adult Henoch schonlein purpura

Biopsy findings in IgA nephropathy 00:10:20

- mesangial proliferation.
- under immunofluorescence– mesangial IgA with or without C3.
- In 1/3 of patients–IgA nephropathy progress to CKD.
- In 1/3 of patients–there is stable course
- In 1/3 of patients–resolves(indication to start steroids)
- MESTC SCORE:

  M – mesangial hypercellularity → Normal
  E – Endocapillary hypercellularity → High activity
  S – Segmental sclerosis }
  T – Tubular atrophy } → CGN
  C – Crescents → RPGN

Treatment of IgA nephropathy 00:14:07

- General management:
  - Control of HTN & proteinuria:
    - ACE ⊖
    - Avoid high proteins
- If there is
  - proteinuria after 6 months of treatment (> 1 gm/day)/
  - Endocapillary Hypercellularity

    ↳ Start with steroids
- Steroids are also started in RPGN & MCD

PSGN 00:17:32

- Childhood PSGN
- Adult PIGN / IRGN

  (Post infectious / infection related)

Childhood PSGN	Adult PIGN / IRGN
• Group A β hemolytic streptococcus Strains 1, 4, 12, 49.	• MRSA
• Throat infection → incubation period 2-4 wks after	
• Skin infection → 4-6 wks after	
• Immunocompetent children	• Immunosuppressed adults ↳ DM, Diabetic foot
• Children 5 – 7yrs	
• Boys > Girls	• No incubation period
• Antigens: • Nephritis associated plasminogen receptor • Streptococcal pyrogenic exotoxin B	
• Present as acute glomerulonephritis	• present as RPGN type 2
• C_3 low in 90% cases	• C_3 low in 60% cases
• C_3 returns to normal by 8 wks(transiently low c3)	• C_3 returns to normal by 8 wks
• Biopsy not required	• Biopsy required
• 100% Recovery If C3 is not low at 8 weeks post infection/recurrent-biopsy is required.	• Prognosis very bad

- microscopic hematuria may take years to resolve

Microscopy findings

00:25:01

- Light microscopy:
  - Hypercellular glomeruli
  - Endocapillary + mesangial hypercellularity
- Immunofluorescence:(in adults & children)
  - Granular IgG + IgM + C_3 along the capillary wall & mesangium

  - Childhood PSGN → Starry sky pattern
  - Adult PSGN → Rope & garland pattern
- Electron microscopy:
  - Subepithelial electron dense deposits containing IgG + IgM ± C_3
  - 'Camel hump' lumpy bumpy deposits

Treatment of PSGN

00:29:40

- Monitor- blood pressure, volume status, serum potassium levels
- Adult PSGN- steroids & vancomycin (nephrotoxic) both are contraindicated.
- Childhood PSGN:
  - Penicillin G for 7-10 days
  - If allergic to penicillin → Erythromycin

GPS AND ALPORT SYNDROME

Good Pasture Syndrome (GPS) : introduction 00:00:17

- Pulmonary renal syndrome:
  - Rapidly progressive glomerular nephritis + Diffuse alveolar hemorrhage (DAH)
    (Any type of involvement of lung)
- Anti GBM disease:
  - Rapidly progressive glomerular nephritis + DAH + Antibody nonspecifically against GBM
- Goodpasture syndrome:
  - Rapidly progressive glomerular nephritis + DAH (very specifically alveolar Hemorrhage)
- Goodpasture disease:
  - Rapidly progressive glomerular nephritis + DAH + Antibody against NC_1 domain of α_3 chain of
    Type IV collagen

Goodpasture disease : causes 00:03:33

- Association → HLA class 2 → DR_4
- HLA DR_1 & DR7 → Protective
- Precipitative factors:
  - Smoking
  - Hydrocarbon exposure
  - Lung infection
  - Fluid overload
- Clinical presentation:
  - 75% Lung involvement → Cough + hemoptysis ± fever
  - 25% Kidney involvement → Rapidly progressive glomerular nephritis → Bad prognosis
- Confirmation of DAH by
  - Hemosiderin laden macrophages in sputum ← most specific
  - ↑ DLCO
  - Blood in air spaces on bronchoscopy

Biopsy and microscopy findings in GPS

00:09:18

- On Biopsy:
  - Diffuse proliferative glomerular nephritis + Cresent
    → Rapidly progressive glomerular nephritis
- Immunofluorescence:
  - Linear IgG ± C_3 deposits along the capillary wall.
  - Anti GBm ⊕

Treatment of GPS

00:10:54

- If any of the following criteria is satisfied, active management should be done
  i) Pulmonary Hemorrhage
  ii) Serum creatinine < 5.5
  iii) Ⓝ urine output
  iv) Recent cellular cresents
  v) ANCA & Anti GBm ⊕
- Active Rx: $\left.\begin{array}{c}\text{Plasmapheresis (14 cycles)} \\ + \\ \text{Steroids} \\ + \\ \text{Cyclophosphamide}\end{array}\right\}$ 3 months
- If progress to CKD → Kidney transplant

Alport syndrome

00:12:52

- X linked (85%):
  - α_5 chain of type IV collagen
  - Seen in males
  - Females are carriers
  - End stage renal disease by 25–30 yrs
- Autosomal recessive (10%):
  - α_3 or α_4
  - males = Females
  - ESRD by 40yrs
- Autosomal dominant (5%):
  - α_3 or α_4

- Seen in both the sexes

$$\begin{tikzcd}
 & \alpha_3\alpha_4\alpha_5 \arrow[r] & \text{Glomerular basement membrane, eyes, ears} \\
\alpha_1\alpha_1\alpha_2 \arrow[ur, no head] \arrow[dr, no head] & & \\
 & \alpha_5\alpha_5\alpha_6 \arrow[r] & \text{Skin, Tubular basement membrane}
\end{tikzcd}$$

- α_6 chain → Leiomyomatosis
- Immunofluorescence pattern of skin →
  - Defective pattern → α_5 Staining
  - Normal pattern → α_3 or α_4

Clinical presentation of Alport syndrome 00:20:32

- 5 yrs → microscopic hematuria
- 10 yrs → Proteinuria + HTN

  After 10 yrs serum creatinine starts to rise
- 15 yrs → SNHL(High or Low frequency on PTA)
- 20yrs → Ophthalmological manifestation
  - ↳ Dot & fleck Retinopathy ← MC
  - Anterior lenticonus ← most characteristic
  - Oil drop reflex
- 25 yrs → End stage renal disease

Microscopic findings of Alport syndrome 00:24:16

- Light microscopy } Normal
- Immunofluorescence } Normal
- Electron microscopy:
  - Alternate foci of thickening & thinning
  - Splitting & lamellation of lamina densa
  - Basket weave appearance

Treatment of Alport syndrome 00:28:45

- ACE inhibitors
- ARB
- Definitive treatment → Transplantation

Active space

- Alport never recurs after Transplantation
- Post transplant - good pasture Syndrome in 5% cases

Thin basement membrane disease 00:30:35

- Autosomal dominant
- No progression to ESRD
- No external abnormalities
- No proteinuria or hypertension abnormalities
- microscopic hematuria
- Electron microscopy for diagnosis

Warning : Not all points are covered in the notes, especially conceptual explanations. Please use the notes in conjunction with Marrow Edition 4 videos.

Myeloma and amyloidosis 00:34:11

- myeloma:
    - Light chain deposition disease - Kappa light chain
    - Nodular involvement
    - Deposition in capillary tuft
- Amyloidosis:
    - Amyloid deposition in mesangium
    - λ light chains
    - Eosinophil congo red +ve hyaline material
    - Nephrotic syndrome + massive proteinuria
    - Light microscopy → similar to MPGN
    - USG → Large Kidneys
    - Kidneys mc involved in 2° amyloidosis

Active space

AKI

00:00:10

- Causes:
    - Prerenal
    - Renal pathology :
        - VASCULAR
        - Glomerular
        - Tubulointerstitial ← mcc
    - Post renal
- Acute Tubular Necrosis is also called as → Acute tubulo interstitial nephritis

Or

Acute interstitial nephritis

Or

Acute Tubular injury

- Hours → Days → AKI
- Days → weeks → Rapidly progressing Renal Failure → Vascular
    - → Cholesterol embolism
    - Glomerular cause – RPGN ← mcc
    - ATIN(Acute Tubulo Interstitial Nephritis)

Criteria for defining AKI

00:06:01

- RIFLE criteria:
    - R → Risk
      I → Injury
      F → Failure
      L → Loss
      E → End Stage Renal Disease
- It takes into account:
    - S. Creatinine
    - Urine output

- AKIN criteria
- KDIGO classification
  - Stage 1 :
    - Creatinine : 1.5 – 1.9 times the baseline
    - Urine output : < 0.5 ml/kg/hr for 6–12 hrs
  - Stage 2:
    - Creatinine : 2 – 2.9 times the baseline
    - Urine output : < 0.5 ml/kg/hr for 12–24 hrs
  - Stage 3 :
    - Creatinine : • >3 times the baseline
      - >4 mg /dl
      - Requiring dialysis
    - Urine output : Anuria for 12 hrs

Stages of tubular injury 00:09:54

- Part of the nephron most susceptible to tubular injury.

↓

Proximal Straight Tubule / Pars recta / S_3 segment

- Stages:

i) Tubular injury	ii) TG feedback	iii) Recovery
↓ Na$^+$	GFR ↓	↓ Na$^+$
↓ K$^+$	↑ S. K$^+$	↓ K$^+$
↓ Ca^{2+}	↑ P	↓ Ca^{2+}
↓ P	↓ Ca^{2+}	↓ P
After 24 hours S.creatinine increases (↑) - Ⓝ	↓ S. Na$^+$	S. Creat ↓
u/o ↑	S. Creat ↑	u/o ↑
	u/o ↓	

TG : Tubuloglomerular

Causes of AKI 00:15:15

- Sepsis ← mcc
- Ischaemia
- Drugs
- Contrast

- Snake bite
- Pancreatitis
- Abruptio placenta

} Renal cortical necrosis

- Rhabdomyolysis
- Tumor Lysis
- Myeloma cast nephropathy / Light chain cast nephropathy

Prerenal AKI

00:18:14

- Dehydration (volume loss)
  - Hepatorenal syndrome
  - Cardiorenal syndrome

Pre-Renal AKI	Ischaemic ATN
• Urine → Normal	• Urine < Alb - Trace/1+ Casts • Muddy brown • Eosinophilic • WBC cast • Granular
• $\frac{\text{B. urea}}{\text{S. creat}} > 20$	• $\frac{\text{B. urea}}{\text{S. creat}} < 10$
• Urine $Na^+ < 20$ meq/L	• Urine Na^+ - >40 meq/L
• Urine pH → Acidic	• Urine pH - Alkaline
• Urine specific gravity: 1.020-1.030	• Urine specific gravity : 1.010
• $\frac{\text{Urine creatinine}}{\text{Plasma creatinine}} > 40$	• $\frac{\text{Urine creatinine}}{\text{Plasma creatinine}} < 20$
• Urine osmolality : 700 - 800 mosm	• Urine. Osmolality : ≈ 300 mosm
• FeNa = < 1%	• FeNa = > 2%

Creat : Creatinine

FeNa : Fractional Excretion of Sodium

Fractional excretion of sodium (FENa) 00:26:00

- Best parameter to differentiate pre renal vs Ischaemic ATIN

$$FENa = \frac{UNa^+}{U\ creat} \times \frac{P.\ Creat}{P.\ Na^+}$$

- Normal FeNa = 1–2%
- FENa has no value when pt is on diuretics
  - → Then do FE urea/FE uric acid
- ATIN but FENa < 1%:
  - NSAID induced Kidney injury
  - Contrast induced AKI
  - Rhabdomyolysis

New markers for ATIN 00:29:11

- NGAL → Neutrophil Gelatinase Associated Lipocalcin
- KIM → Kidney Injury molecule
- Liver fatty acid binding protein

Sepsis 00:30:11

- mc cause of AKI
- Post operative sepsis → most common in valve replacement surgeries
- Tropical infections →
  - Leptospirosis
  - Scrub Typhus
- Complicated UTI
- Pneumonia
- spontaneous bacterial peritonitis
- Diabetic foot

Drugs 00:32:56

- Dose dependent tubular injury:
  - A → Aminoglycosides, amphotericin B, adefovir
  - C → Cisplatin, cyclophosphamide
  - E → Ethylene glycol
  - S → Salicylates

Dose independent tubular injury:

- Type IV Hypersensitivity
- B → β lactams
- R → Rifampicin
- A → Anticonvulsants, Allopurinol
- N → NSAIDS
- D → Diuretics
- Vancomycin
- Omeprazole
- As it is a hypersensitivity reaction, rash and eosinophilia can also be seen

Dose dependent Intratubular obstruction

- M → methotrexate
- I → Indinavir
- T → Triamterene
- A → Acyclovir
- S → Sulfonamide
- Obstruction leads to Oliguric renal failure

Analgesic nephropathy

00:39:00

- Phenacetin-Aspirin-caffeine
- Females > males
- medullary hypoxia → Papillary necrosis
- Chronic Tubulointerstitial disease
- ↑ risk of uroepithelial malignancies
- Papillary calcifications on CT

NSAID induced kidney disease

00:40:31

- Predominant Prostaglandins in Kidney → • PGI_2 → Cortex
  • PGE_2 → Tubules
- Type IV Hypersensitivity
- COX-1 and COX-2 are both constitutively expressed in Kidney
- COX-2 → Seen only in macula densa
- Features:
  - Oliguric AKI
  - FeNa < 1
  - Seen within few days
  - Reversible (may require steroids)
  - Hyperkalemia

- Complications:
  - Uremia
  - Hyponatremia
  - Hypocalcemia
  - Hyperkalemia
  - Pericardial bleeding
  - Cardiac arrhythmias
  - Acidosis

Contrast induced AKI 00:45:24

- High osmolar contrast
- Occur within 24-48 hrs
- Peaking of S.creatinine → 3-5 days
- S.creatinine normal by 7-10 days
- Excellent prognosis
- Its a non oliguric Renal failure

main mechanism of pathogenesis :

-medullary hypoxia

-Direct tubular injury

- Histopathology:
  - Vacuolar changes in PCT
- Preventing of CI-AKI:
  - Fluids → Isotonic saline or sodium bicarbonate (1 ml/kg/hr)
  - Started at least 1hr before & continued for 3-6 hrs afterwards
  - Low volume low osmolar contrast
  - N-acetyl cysteine
- Nephrogenic systemic fibrosis:
  - Seen in patient who's given gadolinium with GFR < 30 ml/min

Uric acid nephropathy /tumor lysis syndrome 00:51:45

- Leukemia / Lymphoma
- CML
- Oliguric AKI
- Intratubular obstruction by uric acid crystals
- ↑ K^+, ↑P, ↑ Mg^{2+}
- ↑S.Creatinine
- ↓ Ca^{2+}

- Rx:
  - Hemodialysis / Rasburicase
- Prevention:
  - Reduce counts by Hydroxyurea
  - Hydrate aggressively 4-6 lts
  - Alkalinize urine → sodium bicarbonate
  - Allopurinol
  - Hemodialysis/Rasburicase

Rhabdomyolysis

00:55:39

- Heme pigment nephropathy
- myoglobin $t_{1/2}$ → 3 hrs
- Heme pigment → PCT injury + vasoconstriction
- Pigmented granular cast
- Oliguria
- Renal failure
- Causes:
  - Crush injury /Electric shock
  - Seizure
  - Exertion
  - Toxins → Alcohol, cocaine, Amphetamines, Heroin
  - Drugs → Fibrates, statins, Zidovudine, Theophylline
  - Infections → Leptospira, coxsackie, Influenza
  - Hypokalemia, Hypophosphatemia
  - Recurrent → mcArdles disease (GSD 5)
  - Hypothyroidism
  - Polymyositis / Dermatomyositis
- Features:
  - muscle pain
  - High coloured urine
  - Hyperkalemia
  - Hypermagnesemia
  - Hyperphosphatemia
  - Hypocalcemia
  - ↑ CPK-MB (peaks by 24 hrs)
  - High anion gap metabolic acidosis
  - ↑ uric acid
  - s. Creatinine ↑

- Treatment:
  - Give large amounts of fluid (5-6 lts)
  - Alkalinize urine
  - Hemodialysis

Snake bite, abruption, pancreatitis 01:04:09

- Leads to Renal cortical necrosis
  - ↳ Coagulative necrosis
  - Loss of viable structures
  - Preserved architecture
  - Karyorrhexis
  - On CT scan: Reverse rim sign – Non enhancing cortex with normal medulla
- Treatment : Once cortical necrosis sets in – Permanent hemodialysis or Renal Transplant

Myeloma 01:06:31

- Light chain cast nephropathy
- Overflow proteinuria
- Glomerulus →
  - Light Chain Deposition Disease – Characterised by Kappa deposits
  - Nodules

Atheroembolic renal disease (cholesterol embolism) 01:07:30

- Extensive atherosclerosis after endovascular intervention --> 30%
- Anticoagulation
- Spontaneous
- Subcute renal failure > RPRF(Rapidly progressive renal failure)
- Livedo reticularis: mottled lower limb
- On Kidney biopsy: BIrefringent Biconvex cholesterol crystals with biconcave clefts within lumen of small vessels
- Hollenhorst bodies

- Diagnosis:
  - LDH ⊕ ⊕
  - CK ⊕ ⊕
  - Eosinophilia
  - ESR/CRP/WBC/Amylase ↑
  - Low complements
  - Birefringent bioconvex cholesterol crystals
  - Risk for ESRD → minimal
  - ACE inhitors are useful

Cardio renal syndromes 01:12:54

- Type I → Acute cardiorenal: → ACS → AKI
- Type II → Chronic cardiorenal: CCF → worsening of renal function
- Type III → Acute renocardiac: AKI → Acute cardiac insult
- Type IV → Chronic Renocardiac: CKD → CAD
- Type V → DM / SLE → Cardiac & Renal diseases

ACS : Acute Coronary Syndrome

CCF : Congestive Cardiac Failure

AKI : Acute Kidney Injury

CKD : Chronic Kideny Disease

HEREDITARY AND CHRONIC TUBULOINTERSTITIAL DISEASE

Chronic tubulointerstitial disease : Causes 00:00:10

- Hereditary:
  - Autosomal dominant polycystic Kidney disease(ADPKD)
  - Autosomal recessive polycystic Kidney disease(ARPKD)
  - Juvenile nephronophthisis
  - medullary cystic disease of Kidney(autosomal dominant)
- Drugs:
  - Analgesic nephropathy
  - Lithium
  - Chinese herbs → Aristolochic acid nephropathy
  - CNI – Cyclosporine, Tacrolimus
    on histology- striped interstitial fibrosis
  - Lead →
    - Hyperuricemia
    - Saturnine gout
  - Cadmium → Ouch ouch nephropathy
- VUR → Reflux nephropathy

Metabolic:

  - Hypercalcemia
  - Hypokalemia
  - Hyperuricemia
  - Hyperoxaluria
- Autoimmune:
  - Sjogren's
  - Sarcoidosis
- Sickle cell anemia

Clinical presentation of CTID 00:04:54

- Asymptomatic for long periods
- No edema
- No HTN
- No hematuria
- Good urine output.
- Rate of fall of GFR → 2-4 ml/min/yr
- Anemia at a very early stage
- B/L small Kidneys
- Polyuria, nocturia
- Proximal tubular wasting →
    - Glycosuria
    - Aminoaciduria
    - Phosphaturia acidosis → causes bone disease
- Type IV RTA → Hyperkalemia
- Nephrogenic diabetic insipidus
- HTN(in later stages)
- Tubular disorder doesn't recur after transplant

ADPKD 00:10:58

- PKD_1 → Chromosome 16 – 85% → Polycystin 1
- PKD_2 → Chromosome 4 – 15% → Polycystin 2
- 90% → Autosomal dominant
- 10% → Spontaneous mutation
- $ADPKD_2$ tends to have late onset & slower progression
- RFT → Normal
- Incidental finding by ultrasound
- 60% develop ESRD by 60yrs
- To prevent the progression of disease:
    - Drink plenty of H_2O
    - Tolvaptan → ADH antagonist
    - criteria to donate the Kidney for transplantation-no single cyst on the Kidney on MRI by the age of 30 yrs.

Diagnosis of ADPKD 00:14:32

- Ravine's criteria:
    - 15 – 29 yrs } ≥ 3 cysts U/L or B/L
    - 30 – 39 yrs } ≥ 3 cysts U/L or B/L

- 40 – 59 yrs → ≥ 2 cysts B/L
- ≥ 60 yrs → ≥ 4 cysts B/L

Complications of ADPKD

00:16:00

- Cyst rupture → Peritonitis
- Uric acid stones > Calcium oxalate stones
- Cyst infections → E.coli.
  - ↳ treatment :
    - Carbapenem
    - Ciprofloxacin
    - Cotrimoxazole
- Extrarenal complications:
  - Hepatic cyst ← mc
  - Colonic diverticula
  - Saccular aneurysm of the anterior circulation → intervention required if-Berry aneurysm > 10mm
  - mitral valve prolapse
  - AR/ Aortic root dilatation
  - Abdominal wall / Inguinal Hernia
  - In few cases pretransplant nephrectomy is required.

ARPKD

00:19:30

- PKHD 1 gene
- Chromosome 6
- Fibrocystin (Polyductin)
- missense mutation(mc type)
- 30% truncating mutations are severe type of mutations→ Only cysts
  - ↳ In adolescence → Congenital Hepatic fibrosis(mcc of death)
  - <3% → Survive above 20yrs → CKD
- 70% → In utero cysts
  - Pulmonary Hypoplasia + Potters facies
  - Small medullary cysts
  - mortality within 1yr
  - Hypertension- present in almost all the cases.

Juvenile nephronophthisis 00:21:42

Juvenile nephronophthisis	medullary cystic kidney disease
• NPHP$_1$	• MCKD$_1$ → Chr 1
• Nephrocystin	• MCKD$_2$ → Chr 16
• Autosomal recessive	• Autosomal dominant
• Chromosome 2	• Uromodulin
• 6-7 yrs of age	• 20-25 yrs of age
• ESRD by 13 yrs	• ESRD by 40-45 yrs
• Tubular basement membrane irregularities	• Tubular BM irregularities
• Tubular cyst	• Tubular cyst
• Tubular atrophy	• Tubular atrophy
• Salt wasting, polyuria	• Salt wasting, polyuria
failure to thrive, Rickets	
• Extrarenal manifestation:	
• Retinitis pigmentosa	• Hyperuricemia & gout
• Situs inversus	• Insulin resistance
-Cerebellar manifestations	•treatment-transplantation
•treatment-transplantation	

Medullary sponge kidney 00:25:17

Sporadic

- Never goes to CKD
- Recurrent UTI ← mc symptom
- Recurrent stones
- Recurrent hematuria
- Dilated & spongy CD
- Distal RTA
- Hypercalciuria
- Calcium phosphate stones

- On excretory urogram → Paint brush appearance
- On IVU → Bunch of grapes or papillary blush

Nephrocalcinosis: Causes

00:29:34

- Causes of Medullary Nephrocalcinosis:
  - Hypercalcemia:
    - Sarcoidosis
    - Hyperparathyroidism
  - Tubular disorders
    - Distal RTA
    - Bartter Syndrome
  - Medullary sponge Kidney
  - Acetazolamide, Amphotericin-B
- Cause of Cortical Nephrocalcinosis:
  - CKD
  - Renal TB
  - Cortical necrosis
- Causes of both Cortical & Medullary Nephrocalcinosis:
  - Oxalosis

Active space

CKD : causes 00:01:39

Causes:	Rate of fall of GFR
Diabetic nephropathy	→ 8 – 10 ml/min/yr
Chronic glomerulo nephritis	→ 6 – 8 ml/min/yr
Ischaemic nephropathy	→ 4 – 6 ml/min/yr
Chronic tubulo interstitial disease	→ 2 – 4 ml/min/yr
ADPKD	→ 1 – 2 ml/min/yr

Grading of CKD 00:04:14

- Grade 5:
  - < 15ml/min ← GFR
  - ESRD
  - Uremic phase
- Grade 4:
  - 15 – 29 ml/min
- Grade 3:
  - 30 – 59 ml/min →
    - 30– 44 → 3b
    - 45– 59 → 3a
- Grade 2:
  - 60 – 89 ml/min
- Grade 1:
  - >90 ml/min
  - Biochemical / Histological / Radiological evidence of Kidney disease
- A_1 → Alb/creat → < 30 mg/g
- A_2 → 30 – 300 mg/g
- A_3 → > 300 mg/g

Issues with respect to CKD 00:06:49

- Anemia
- Vascular + cardiac disorders
- Bone mineral disease
- Hyperkalemia
- Fluid status disturbance
- Uremia
- Endocrine & skin manifestation

- CAD → mcc of death in CKD
- Strongest risk factor for progression of CKD → Proteinuria
- morphological predictor of CKD progression → degree of tubulo interstitial involvement

Anemia in CKD 00:11:29

- < 10g/dl in CKD
- Target Hb to be achieved → 11 g/dl
- Never more than > 13g/dl → ↑ risk of stroke
- Anemia starts appearing in CKD stage 3 onwards
- Anemia independently ↓ GFR
- Progression of LVH

  ↓

  Diastolic heart failure

  ↓

  ↑ Cardiovascular mortality
- Causes for anemia in CKD:
  - Absolute or relative deficiency of erythropoietin
  - Erythropoietin : produced by fibroblasts in interstitium (cortex and outer medulla)
    produced on response to HIF (Hypoxia Inducible Factor)
    acts on JAK2 receptors
  - Anemia of chronic disease
  - Iron deficiency anemia
  - ↑ PTH → bone marrow fibrosis
  - Uremia → bleeding
  - B_{12}, folate & nutritional deficiencies
  - Hemoglobin – 8 gm/dl

    TC } Normal
    Platelet } Normal

Hypo-proliferative	Hyper-proliferative
-Reticulocyte production index < 2	Reticulocyte production index : > 2.5 -CKD

- Serum ferritin – Decreased
- % Saturation of Transferrin – Decreased
- % Saturation of Transferrin= $\frac{\text{serum ferritin}}{\text{TIBC}} \times 100$

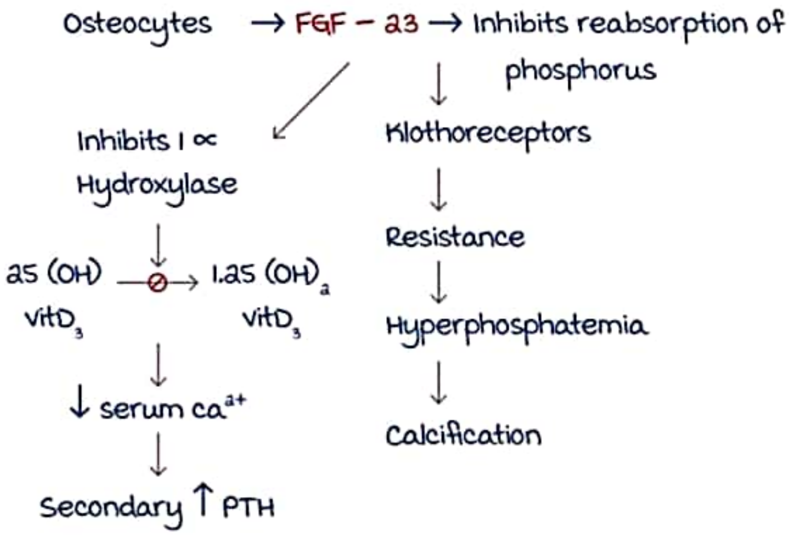
Management of anemia in CKD 00:21:47

- Step 1: Iron therapy
- It should be started when → • S. ferritin ≤ 500ng/ml
  - PSAT ≤ 30%
- Parenteral iron formulations →
  - Iron Sucrose 200mg
  - Ferric carboxymaltose 1 gm
  - Ferric isomaltose 1.5 gm
- Iron deficit = $2.2 \times Bw \times (14 - Hb) + 1000$
- Step 2: Erythropoietin therapy
  - Using • Recombinant human erythropoetin.
    20-50 units /kg /3times /week s.c / i.v.
    Or
    - Darbepoetin alfa
      Advantages of Darbepoetin Alfa :
      - Long T1/2
      - Increased carbohydrate content .
      - more Sialic Acid resistance
    Or
    - methoxy Polyethylene glycol epoetin beta. (CERA)
- Problems of giving erythropoietin → • Stroke
  - MI
  - HTN

Vascular and bone mineral diseases in CKD 00:28:28

- Accelerated atherosclerosis:
  - ↑ Oxidised LDL, ↑ LP(a)
  - Loss of fetuin in urine
  - ↑ asymmetrical dimethyl arginine
  - ↑ PTH → Atherogenic
  - Statins arenot routinely recommended in CKD
- Calcification:
  - Irreversible
  - Diffuse medial calcification → PTH
  - Infimal calcification → PTH independent

- Hyperphosphatemia
  - Converts Endothelial cells → Osteoblasts
  - Irreversible calcification
  - It is due to ↓ nephron number
- In stage 3,4 of CKD,
  - Phosphatonin → Excrete phosphorus



Osteocytes → FGF – 23 → Inhibits reabsorption of phosphorus

FGF – 23 → Inhibits 1 ∝ Hydroxylase → 25 (OH) $VitD_3$ ⊘→ 1.25 $(OH)_2$ $VitD_3$ → ↓ serum ca^{2+} → Secondary ↑ PTH

FGF – 23 → Klothoreceptors → Resistance → Hyperphosphatemia → Calcification

High and low bone turnover state

00:36:13

- High bone turnover state

Increased PTH

Secondary Hyperparathyroidism.	Tertiary Hyperparathyroidism
	PTH(> 1500pg/ml)
↓ calcium	↑ calcium
↑ PTH	
↑ Phosphorous	↑ Phosphorous

- High bone turnover state:
  - ↑ PTH →
    - ↑ Bone formation
    - ↑ Bone resorption
    - No time for mineralization
  - $Ca(OH)_2$ appatite → $CaPo_4$
    ↓
    - Early fracture
    - Bone pain
    - ↑ Bone marrow fibrosis
    - Diffuse medial calcification
    - Osteitis fibrosa cystic

- Subperiosteal resoption on the radial side of the proximal and middle phalanges of 2^{nd} & 3^{rd} fingers
- Browns tumor (Localised collection of macrophages)
- Low bone turnover state/Adynamic bone disease
    - 10%
    - Females
    - Caucasians
    - Diabetics
    - Peritoneal dialysis
    - ↑ Risk for fracture, calcifications
    - ↑ Ca^{2+}
    - Ca^{2+} supplements
    - Vit D } ↓ PTH
    - High Ca^{2+} dialysate
    - Aluminium

Warning : Not all points are covered in the notes, especially conceptual explanations. Please use the notes in conjunction with Marrow Edition 4 videos.

Management of high and low bone turn over state 00:42:01

- Rx of High Bone turnover:
    - Correction of Hyperphosphatemia:
        - Phosphate binders →
            - Sevelamer
            - Lanthanum
            - Sucroferric oxyhydroxide
    - Correction of ↑ PTH:
        - Calcium sensing receptor agonist → Cinacalcet
        - Used only if S.Ca^{2+} > 9.5 mg/dl
- In Low Ca^{2+}, ↑ Phosphorous state → Calcium containing PO_4 binders
- In Low Ca^{2+}, Low Phosphorous → VitD. 60,000 IU once a week × 6 doses Or calcitriol
- Rx of Low bone turnover:
    - Cutoff all calcium supplements

Indications for parathyroidectomy in CKD 00:53:54

- Refractory Hypercalcemia and Bone diseases
- Refractory pruritis
- Severe calcification

Cardiac manifestations in CKD 00:55:03

- Accelerated Atherosclerosis
- Calcification
- Acute Coronary Syndrome
  - → TROP I
  - Inducible test →
    - Treadmill test
    - Dobutamine stress echo
  - Angiogram

Nervous system manifestations in CKD 00:58:05

- Uremic encephalopathy
  - GFR < 10 ml/min
  - Altered sensorium, gait & speech abnormalities
  - 100% response to dialysis
  - due to guanidosuccinic acid

- Uremic Neuropathy:
  - Small fibre, distal to proximal involvement
  - Sensorimotor
  - Lower limp predominatly involved
  - Polyneuropathy

- Aluminium → Dialysis dementia

Endocrine dysfunctions in CKD 01:00:43

- Hypoglycemia:
  - Half life of insulin prolonged
  - ↓ renal glucongenesis

- ↑ TG
- ↓ HDL
- ↑ Oxidised LDL
- ↑ LP(a)
- ↑ apo B, apoc

- LDL Ⓝ
- Malnutrition inflammation atherosclerosis (MIA)
- ↑ Prolactin
- ↓ Testosterone/Estradiol.
- ↑ FSH/↑ LH
- ↑ Cortisol
- ↑ GH, ↓IGF
- ↑ T_4, ↓ T_3, ↑ rT_3

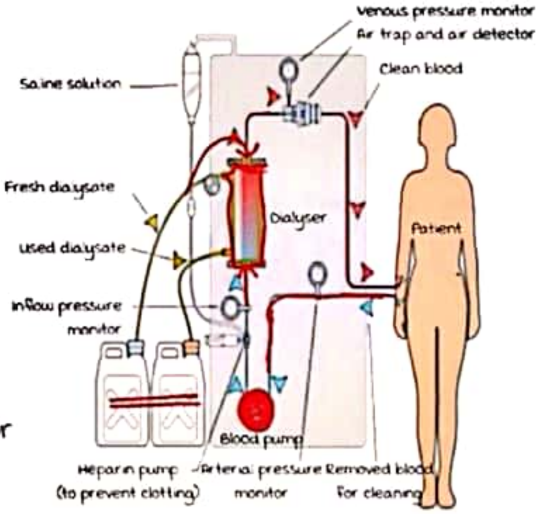
Skin changes in CKD 01:04:50

- Xerosis
- Uremic purities:
  - Rx:- Opioid κ agonist → Nalfurafine
- Prurigo nodularis
- Calcific uremic arteriopathy / Calciphylaxis
  - ↳ Occlusion of dermal vessels → Severe skin necrosis
  - Precipitated by warfarin
  - Rx :
    - Sodium Thiosulfate
    - Vit K
    - Stop Ca^{2+}

Active space

Hemodialysis machine & Circuit 00:00:40

- Fresenius F6 machine
  - Blood access
  - Blood tubing
  - Blood pump
  - Dialyser
  - Air traps
  - Air detectors
  - Pressure monitors
    “Arterial monitor
    “venous monitor”
  - Syringe pump
  - Blood leak detector


Venous pressure monitor
Air trap and air detector
Clean blood
Saline solution
Fresh dialysate
Dialyser
Patient
used dialysate
inflow pressure monitor
Blood pump
Heparin pump (to prevent clotting)
Arterial pressure monitor
Removed blood for cleaning

- Blood flow rate: 300–500 ml/min
- Dialysate flow rate: 500–800 ml/min
- Recommended dialysis → 3 times/week
- Each session → 4 hr duration
- 1st session → 2 hr duration

Access for hemodialysis 00:05:57

- Arteriovenous fistula → Long patency, least chance of infection
- Arteriovenous graft
- Central venous catheter (cuffed tunneled permeability catheter)
  → Rt IJV > Lt IJV > Rt. Subclavian

Arteriovenous fistula 00:07:03

- Preferred form
- Types:
  - Left Radiocephalic fistula (Brasica cimino) ← 1st choice
  - Lt Brachiocephalic fistula
  - Lt Brachiobasilic fistula

- Rule of 6 in fistula:
    - 6 mm in diameter
    - < 6 mm from skin surface
    - Blood flow → 600 ml/min, minimum flow
    - 6 wks for maturation
    - Straight 6cm long segment for cannulation

- Venous end of fistula → Directed towards heart
- Arterial end of fistula → Directed towards anastomosis

- Signs of maturation of fistula:
    - Large vein
    - Prominent thrill
    - Strong bruit
    - 6 cm straight segment

Changes taking place across the dialyser 00:10:23

- Diffusion

Ultrafiltration (convection):

↳ Water is moving from a state of higher concentration to lower concentration, at the same dragging all the molecules with it which are less than the pore size

High efficiency dialysis (KoA):

- At infinity high blood flowrate & dialysis flow rate, how much amount of solute can be cleared
- ml/min
- >800 ml/min

High flux dialysis (Kuf):

- For a given mmHg gradient → the fluid removed per hr
- >20 ml/hr/mmHg

Middle molecules 00:15:18

- 500-20,000 D_a
- more than the pore size
- Cannot be removed by conventional dialysis
- Can be removed by High flux dialysis

Example:
  - Aβ2 microglobulin
  - Vit B12
  - FGF – 23
  - Leptin
  - middle molecules in diabetic neuropathy.

Dialyzer and dialysate 00:17:12

- Hollow fiber synthetic dialyzer
- made of Polyacrylonitrile / Polysulfone

- Dialysate:
  - Bicarbonate buffer
  - Potassium → Rule of seven → Dialysate + $S.K^+ = 7$
  - $Ca^{2+} \rightarrow 2.5 - 3.5$ meq/l

Complications during dialysis 00:19:12

- Intradialytic Hypotension: ← mc
  - Due to
    - Volume changes
    - Cardiac factors
    - Lack of vasoconstriction
- muscle cramps
- Dialyser reaction
- Dialysis disequilibrium syndrome → most dangerous

Dialysis disequilibrium syndrome 00:21:10

- Cerebral edema due to rapid removal of all the urea
- Sudden shift in osmolarity
- Water moves from Blood → Cerebral space
- Prevention
  - 1st session → 2hr duration
  - Urea reduction ratio < 40%
  - Blood flow rate → 150 – 200 ml/min
  - Never use high efficiency dialyser
  - No more than 2 lts of ultrafiltrate removed

Active space

Use of heparin in dialysis 00:23:28

- 1000 units bolus
- 500 units/hr
- Stop 1 hr before the end of dialysis
- monitored by : apTT (150% raise)
- Antidote : Protamine sulfate

Peritoneal dialysis 00:26:29

- Advantages Over Hemodialysis:
  - Easy access
  - Children → ↑ peritoneal surface area
  - ↓ risk of cardiac complication
  - No role in hyperkalemia
  - Better anemia correction

- Phenomenon of working of PD → Three pore model
  - Large pores (20 – 40 nm)
  - Small pores(4 – 6 nm)
  - Ultra pores (<0.8 nm) → Aquaporins

- Peritoneal dialysis solution:
  - Balanced buffered salt solution
  - Predominantly made of dextrose
  - No K^+
  - Lactate buffer

Renal transplantation 00:28:34

- HLA matching based on HLA → A, B, DR
- 4/6, 5/6, 6/6 match → No induction therapy
- 3/6 → minimal induction
- 2/6, 1/6, 0/6 → Induction

- Induction agents:
  - In 2/6, 1/6, 0/6 → Depleting agents
    - Rabbit Antithymocyte globulin
    - OKT_3
    - Almetuzumab

- In 3/6 → Non depleting agents
  - ↳ Basiliximab (Anti CD – 25)

- Maintainance therapy:
  - Steroids + mycophenolate mofetil + Tacrolimus
    Or
    Cyclosporine
  - Reserve drug → m to R inhibitor → Sirolimus
- Advantages of Tacrolimus:
  - No Hirsuitism
  - No gingival hyperplasia
  - No Hyperuricemia
  - No Hyperlipidemia
- Disadvantages of Tacrolimus:
  - DM
  - Tremor
  - Alopecia

Graft rejection

00:35:49

- 2 Types:
  - Acute T cell mediated rejection:
    - mc
    - Tubulointerstitial pattern (Tubulitis)
    - Vascular pattern (endothelitis)
    - Good prognosis
    - Rx : Steroids
- Acute antibody mediated (B cell) rejection:
  - Peritubular capillaritis
  - CD4 +ve
  - Donor specific antibody ⊕
  - Bad prognosis
  - Rx : Plasmapheresis + Rituximab

Active space

Post transplant infections 00:37:26

- Donor derived infections.
- Recipient derived infections.
- Nosocomial infections.
- Community infections.

- Infection in 1st month post transplant:
  - Surgical scar / wound / Catheter infections
  - Candida infections

- Infections 1-6 months after transplant:
  - Opportunistic infections:
    - CMV
    - EBV
    - HBV
    - HCV
    - PCP
    - Aspergillus
    - Listeria

- Infections >6 months after transplant
  - Chronic viral infections → BK polyoma virus
  - PCP
  - Nocardia
  - Listeria
  - Aspergillus

BK polyoma virus 00:39:14

- ds DNA virus
- Produce post transplant infections < 1yr
- Asymptomatic
- Ureteric obstruction
- Tubulo interstitial nephritis
- In the urine → Decoy cells
- Diagnosis → Cytopathic changes + SV 40 Antigen +ve

- Rx:
  - Reduce immunosuppression
  - Leflunomide
  - Cidofir
  - IVIG
  - Quinolones

CMV infection

00:41:00

Donor	Recipient	CMV Antibody status			
		Terminology	Infection %	Disease %	Pneumonitis %
+	–	Primary infection	70 – 88	56 – 80	30
–	+	Reinfection	0 – 20	0 – 27	Rare
+	+	Reinfection or superinfection	70	27 – 39	3 – 14
–	–	–	0	–	0

- Symptomatic acute CMV infection:
  - CMV Syndrome :
    - Fever
    - Leukopenia
    - Thrornbocytopenia
- Invasive CMV disease:
    - Pneumonitis
    - Hepatits
    - Enterocolitis
- Histopathology:
  - Intranuclear owl eye inclusion bodies
- Rx:
  - IV ganciclovir for 2 –3 wks

    Or

    Vanganciclovir for 21 days
- Prophylaxis:
  - Valganciolouir for 200 days